No. 01-1151

IN THE

United States Court of Appeals

FOR THE FEDERAL CIRCUIT

RANBAXY PHARMACEUTICALS INC.,

Defendant-Appellant,

v.

GLAXO GROUP LIMITED and
GLAXO WELLCOME, INC.,

Plaintiffs-Appellees.

APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY IN CIVIL ACTION NO. 00-5172,
JUDGE MARY LITTLE COOPER

NONCONFIDENTIAL BRIEF OF DEFENDANT-APPELLANT RANBAXY PHARMACEUTICALS INC.

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January 9, 2001

CERTIFICATE OF INTEREST

Counsel for the Appellant Ranbaxy Pharmaceuticals Inc. certifies the following:

1. The full name of every party represented by me is:

   Ranbaxy Pharmaceuticals Inc.

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is:

   Not Applicable

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party represented by me are:

   Ranbaxy Pharmaceuticals Inc. is a wholly-owned subsidiary of Ranbaxy [Holdings] UK Ltd. which is a wholly-owned subsidiary of Ranbaxy Netherlands B.V. which is a wholly-owned subsidiary of Ranbaxy Laboratories Limited.

4. The names of all law firms and the partners or associates that appeared for the party now represented by me in the trial court or agency or are expected to appear in this Court are:

   Knobbe, Martens, Olson & Bear, LLP; Darrell L. Olson; William R. Zimmerman; Mathews, Collins, Shepherd & Gould, P.A.; and Ronald Gould.

Date: 1/8/01

By: _____
Darrell L. Olson
Counsel for Defendant-Appellant
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MATERIALS DELETED FROM THE NON-CONFIDENTIAL BRIEF OF DEFENDANT-APPELLANT RANBAXY PHARMACEUTICALS INC.

Materials omitted on p. 61:

- Glaxo's estimated potential first year loss

Materials omitted on p. 63:

- Glaxo's sales of Ceftin® in the United States since launch

Materials omitted on JA 17-18:

- Glaxo's sales of Ceftin® and estimated first year loss in market share and dollars

Materials omitted on JA 44:

- Glaxo's sales of Ceftin® and estimated first year loss in market share and dollars

STATEMENT OF RELATED CASES

There has been and is no other appeal from the present civil action in this or any other appellate court. Counsel is aware that Glaxo Group Ltd. and Glaxo Wellcome, Inc. (collectively "Glaxo") have filed suit against Apotex Inc. alleging infringement of the same patent that is at issue in this appeal. *See Glaxo Group Ltd. v. Apotex Inc.*, Docket No. 00 C 5791 (N.D. Ill.). Counsel is unaware whether this Court's decision in this appeal will directly affect the suit against Apotex Inc.

STATEMENT OF SUBJECT MATTER AND APPELLATE JURISDICTION

The statutory bases for jurisdiction of the United States District Court for the District of New Jersey in this declaratory judgment action for patent infringement are 28 U.S.C. § 1338(a) and 28 U.S.C. §§ 2201, 2202. Pursuant to 28 U.S.C. § 1292(c)(1), this Court has jurisdiction over this interlocutory appeal from the grant of a preliminary injunction.

The district court entered an order granting a preliminary injunction on December 21, 2000. JA 1-2. Appellant timely filed notice of appeal from the grant of the preliminary injunction on December 21, 2000. JA 1718-19; *see* Fed. R. App. P. 4(a)(1).

I. STATEMENT OF THE ISSUES

1. Did the district court err as a matter of law in construing Claim 1 of U.S. Patent No. 4,562,181?

2. Did the district court err in finding a likelihood of success on infringement under its claim construction, in assessing the other preliminary injunction factors in light of its likelihood of success finding, and in granting a preliminary injunction based upon these findings?

II. STATEMENT OF THE CASE

A. Nature Of The Case

Ranbaxy Pharmaceuticals Inc. ("Ranbaxy") appeals from the district court's grant of a preliminary injunction, which the district court premised on its erroneous construction of Claim 1 of U.S. Patent No. 4,562,181 ("the '181 patent").

B. Statement Of Facts

1. Glaxo's Cefuroxime Axetil Patents And Ceftin® Product

The '181 patent, at issue in this appeal, is directed to a specific physical form of the antibiotic cefuroxime axetil. JA 67 (col. 2, ll. 20-22) ("cefuroxime axetil is advantageously prepared and used in highly pure amorphous form rather than in crystalline form."), 73 (Claim 1). The '181

patent alleges the narrow improvement that the amorphous form of cefuroxime axetil provides advantages over the crystalline form. JA 67 (col. 2, ll. 1-22).

On May 12, 1981, Glaxo Laboratories Limited obtained U.S. Patent No. 4,267,320 ("the '320 patent") directed to a family of cephalosporin antibiotics, including cefuroxime axetil. JA 856-57. Pursuant to 35 U.S.C. § 156, Glaxo Laboratories Limited obtained a two-year patent term extension for the '320 patent, the maximum permissible extension. JA 866-68. Thus, the '320 patent expired on May 12, 2000, placing cefuroxime axetil in the public domain and ending Glaxo Laboratories Limited's exclusivity over the compound cefuroxime axetil. JA 856, 868.

The '320 patent, which is prior art to the '181 patent, discloses that esters of the antibiotic cefuroxime possess beneficial properties over other cefuroxime compounds. JA 857. The '320 patent recites cefuroxime axetil, a particular ester of cefuroxime, as "particularly preferred" and expressly claims this compound in Claim 4. *Id.*; JA 858 (col. 3, ll. 10-11), 864 (Claim 4). The '320 patent also specifically discloses the oral administration of cefuroxime axetil as an antibiotic. JA 856, 857 (col. 2, ll. 12-31).

Cefuroxime is a broad spectrum antibiotic that is used to treat various conditions, including pharyngitis, tonsillitis, acute bacterial maxillary sinusitis, and skin infections. JA 6, 275-77. Cefuroxime axetil delivers the active drug substance cefuroxime, also referred to as the active moiety, to the patient. JA 15, 41, 67-68, 673 (Ternyik Decl., ¶¶ 3, 6). The active moiety provides the beneficial medicinal properties of the antibiotic.

Cefuroxime axetil can exist in two physical forms: (1) the amorphous form, in which the molecules are not in an ordered arrangement, and (2) the crystalline form, in which the molecules are in an ordered arrangement. JA 67 (col. 1, line 62 - col. 2, line 22), 1639-40 (Lancaster Decl., ¶¶ 4-5). The '181 patent, which issued to Glaxo on December 31, 1985 and which expires on June 29, 2003, alleges a narrow improvement over the '320 patent. JA 64, 67. The '181 patent discloses that the amorphous form of cefuroxime axetil provides advantages over the crystalline form. JA 67 (col. 2, ll. 20-22).

Claim 1 of the '181 patent recognizes this distinction between the two physical forms by narrowly claiming the amorphous form to the virtual

exclusion of the crystalline form.[1] Claim 1 of the '181 patent, the only independent claim, recites:

> Cefuroxime axetil in amorphous form essentially free from crystalline material, and having a purity of at least 95% aside from residual solvents.

JA 73 (emphasis added). The emphasized portion of Claim 1 is the disputed claim limitation both before the district court and in this appeal.

During the extended period of exclusivity provided by the '320 patent, the FDA approved Glaxo Wellcome, Inc.'s New Drug Application ("NDA") for a cefuroxime axetil antibiotic. JA 200 (Rivera Decl., ¶¶ 2-3), 870, 881, 1165. In 1988, Glaxo began to market Ceftin®, the commercial embodiment of the '320 patent and the '181 patent, under this NDA. JA 200 (Rivera Decl., ¶ 2-3), 1199 (Glaxo marks the package insert for Ceftin® with the '320 and '181 patent numbers). Glaxo claims that Ceftin® is entirely amorphous and contains no crystalline material. JA 201 (Rivera Decl., ¶ 5), 1165, 1167, 1180-81 (the U.S.P. monograph for cefuroxime axetil states that

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[1] The written description of the '181 patent reinforces this distinction between the amorphous and crystalline forms, stating that the amorphous form should be prepared to "avoid formation of any crystalline material." JA 68 (col. 4, line 46) (emphasis added).

"It is amorphous."). In an effort to preserve and extend exclusivity over cefuroxime axetil, in addition to the '181 patent, Glaxo also filed and obtained several patents on processes for preparing cefuroxime axetil and on coatings for cefuroxime axetil tablets prior to expiration of the '320 patent. JA 1218-27, 1232-41, 1245-89. Glaxo does not assert any of these other patents against Ranbaxy. JA 1299-1301.

2. Ranbaxy's Cefuroxime Axetil Antibiotic

Ranbaxy is a New Jersey based company engaged in the development and marketing of both innovative and generic pharmaceuticals. JA 677. On April 19, 1999, Ranbaxy's parent company, Ranbaxy Laboratories Limited, filed an Abbreviated New Drug Application ("ANDA") with the Food and Drug Administration ("FDA") seeking approval to market a generic form of cefuroxime axetil in tablet form.[2] JA 673 (Ternyik Decl., ¶ 2), 677 (Chattaraj Decl., ¶ 3), 870-71. Ranbaxy filed its ANDA in anticipation of the expiration of Glaxo's '320 patent in May of 2000. JA 677.

Under the ANDA process, which was specifically implemented to foster more rapid approval of generic drug products, Ranbaxy need not

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[2] Although Ranbaxy Laboratories Limited filed the ANDA, for ease of reference this brief refers to the ANDA as "Ranbaxy's ANDA."

conduct clinical trials to show the safety and efficacy of its cefuroxime axetil antibiotic. JA 14, 673; *see Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1568, 42 U.S.P.Q.2d 1257, 1262 (Fed. Cir. 1997) (ANDA process fosters "expedited approval"). In order to speed the approval process, Ranbaxy must instead show that the cefuroxime axetil antibiotic that is the subject of its ANDA is bioequivalent to the already-approved drug product of another company, in this case Glaxo's Ceftin® product. JA 14, 673. "Bioequivalence" does not mean that the composition of Ranbaxy's cefuroxime axetil antibiotic is the same as Ceftin®, but rather that Ranbaxy's cefuroxime axetil antibiotic delivers the same amount of the active moiety cefuroxime to the patient as Ceftin®. JA 14-15, 673.

While Ranbaxy's cefuroxime axetil antibiotic is bioequivalent to Ceftin® for purposes of ANDA approval, it differs significantly in composition from Ceftin®. JA 871, 892, 1054. Unlike Ceftin®, which contains no crystalline material, Ranbaxy's cefuroxime axetil antibiotic contains a mixture of crystalline and amorphous cefuroxime axetil. JA 15, 41, 201 (Rivera Decl., ¶ 5), 673 (Ternyik Decl., ¶ 5), 895-97, 927-31, 1047, 1054, 1165, 1167, 1180-81. Ranbaxy's ANDA requires the amount of crystalline cefuroxime axetil to range between 10-15% of the total amount of

cefuroxime axetil, with the balance of 85-90% cefuroxime axetil being amorphous. JA 15, 41, 673 (Ternyik Decl., ¶ 5), 895-97, 927-31, 1047, 1054. In the samples that were used to establish bioequivalence for purposes of the ANDA, Ranbaxy's cefuroxime axetil antibiotic contained 12% crystalline and 88% amorphous cefuroxime axetil. JA 15, 41, 673 (Ternyik Decl., ¶ 5), 1035, 1054. Both the crystalline and amorphous cefuroxime axetil in Ranbaxy's cefuroxime antibiotic deliver the active moiety cefuroxime to the patient. JA 15, 41, 673-74 (Ternyik Decl., ¶ 6). In contrast, Ceftin® contains only amorphous cefuroxime axetil. JA 201 (Rivera Decl., ¶ 5), 1165, 1167, 1180-81. Thus, the two drug products differ markedly in the form of cefuroxime axetil used.

The FDA has not yet approved Ranbaxy's ANDA, and Ranbaxy cannot launch its cefuroxime axetil antibiotic until FDA approval is granted. JA 16, 673 (Ternyik Decl., ¶ 3), 677 (Chattaraj Decl., ¶¶ 4-5). While Ranbaxy cannot predict with certainty when the FDA will approve its ANDA, Ranbaxy believes FDA approval is imminent. JA 16, 46-47, 677 (Chattaraj Decl., ¶ 4), 1325 (Chattaraj Dep. 54:3-6), 1327 (Chattaraj Dep. 61:5-8 (FDA approval expected "Any day now.")). But for the district court's preliminary injunction, Ranbaxy would launch its cefuroxime axetil

antibiotic immediately upon FDA approval. JA 1323 (Chattaraj Dep. 48:18-23).

Glaxo has opposed Ranbaxy's ANDA in the FDA by filing a Citizen Petition and a supplement thereto. JA 1163-1217. Glaxo's Citizen Petition has delayed approval of Ranbaxy's ANDA, which otherwise was expected to occur in late 2000. JA 677 (Chattaraj Decl., ¶ 6).

3. The Current Litigation

In 1999, Glaxo contacted Ranbaxy demanding that Ranbaxy disclose whether it had filed an ANDA for any cefuroxime axetil antibiotic. JA 1290, 1292, 1295-96. Glaxo also demanded that Ranbaxy provide samples of any such drug product and provide the reasons that its drug product does not infringe Glaxo's various patents relating to cefuroxime axetil. *Id.* Ranbaxy responded to Glaxo's letters by acknowledging Glaxo's patents and stating that it did not infringe these patents. However, Ranbaxy refused to disclose its confidential ANDA and product information to Glaxo. JA 1291, 1293-94, 1297-98.

On October 20, 2000, Glaxo filed suit against Ranbaxy in the District of New Jersey seeking a declaratory judgment that Ranbaxy's manufacture and sale of the cefuroxime axetil antibiotic that is the subject of Ranbaxy's

ANDA would infringe the '181 patent. JA 59-63. At Glaxo's request, the district court ordered expedited discovery regarding Ranbaxy's confidential ANDA on November 6, 2000. JA 140-41. Ranbaxy provided the expedited discovery, including producing its confidential ANDA and making the President of Ranbaxy available for deposition. JA 1307-10, 1313.

Without Ranbaxy having been permitted the opportunity to conduct any discovery whatsoever, Glaxo filed a motion for a preliminary injunction on November 21, 2000. JA 166, 185. Glaxo's motion sought to enjoin Ranbaxy from marketing its cefuroxime axetil antibiotic after the FDA approves Ranbaxy's ANDA. JA 166. On December 18, 2000, the district court issued a Memorandum granting a preliminary injunction enjoining Ranbaxy from launching any cefuroxime axetil product under its ANDA. JA 3, 50. On the same date, the district court issued an Order to Show Cause regarding the amount of the preliminary injunction bond or, alternatively, whether the preliminary injunction should be made final obviating the need for a bond. JA 50. Thus, the district court wanted to consider granting a permanent injunction against Ranbaxy thereby ending proceedings in the district court, even though Ranbaxy had not yet been given any opportunity to conduct discovery. *Id.*

The district court entered a Preliminary Injunction Order on December 21, 2000, after the parties agreed as to the entry of a preliminary (not permanent) injunction and the amount of the bond. JA 1-2. The Order enjoined Ranbaxy from launching any cefuroxime axetil product under its ANDA, set a bond of $10,000,000 to compensate Ranbaxy for injury resulting from being wrongfully enjoined and stayed all proceedings in the district court, including the Order to Show Cause, pending this appeal. *Id.* In staying further proceedings, the district court stated that the decision of this Court on appeal "may become dispositive of the litigation here pending," recognizing that this case turns on the legal issue of claim construction discussed in the following section. JA 1717.

4. The District Court's Claim Construction

The district court adopted Glaxo's proposed claim construction and construed "essentially free from crystalline material" in Claim 1 of the '181 patent to mean "merely excluding from the claimed invention any item having sufficient crystalline cefuroxime axetil that materially or fundamentally affects the basic characteristics of the invention." JA 26-27; *see* JA 28, 37-38. The district court's basis for this construction was a dictionary definition of "essentially" as meaning "fundamentally" and a

dictionary definition of "essential" as meaning "belonging to or being a part of the essence of something." JA 27. After reciting these definitions, the court leaped to the conclusion that "essentially free from" focuses "on whether the crystalline material fundamentally affects the characteristics and functions of the cefuroxime axetil invention." *Id.* The court attempted to support its claim construction by noting that it is "consistent" with the meaning of the recognized transitional phrase "consisting essentially of," which excludes elements that would materially affect the characteristics of the invention. *Id.*

In reaching its claim construction, the district court rejected or ignored substantial intrinsic evidence. For example, the '181 patent claims priority to United Kingdom Patent Application No. 8222019, which expressly defines "essentially free from crystalline material" as meaning that the crystalline content is "so low as to be undetectable," i.e., an amount that "may be assumed to be zero for all practical purposes." JA 28, 797, 845. While acknowledging that the UK application was intrinsic evidence and "does perhaps favor a more restrictive interpretation of the claim," the district court rejected the express definition in this priority document because it was not contained in the '181 patent itself, "but only in a 1982

foreign application about which we know very little." JA 28-30, 33. The district court also relied on extrinsic evidence submitted by Glaxo to bolster its decision to ignore this express definition. JA 31-33.

Similarly, the district court next chose to ignore portions the written description of the patent, which contain examples disclosing the "absence of crystals" (Example 1), "the presence of a few crystals" (Example 18) and "< 1% crystalline material" (Example 21). JA 35-36. The district court ignored these teachings "because of the inherent confusion and lack of clarity involved." JA 36.

Finally, the district court ignored portions of the prosecution history of the patent, which contradict the court's claim construction. JA 33-34. Glaxo originally attempted to obtain a broad independent claim to cefuroxime axetil in "substantially amorphous form," and a claim dependent upon such broad independent claim further specifying that the composition was "essentially free from crystalline material." JA 10, 34. However, in response to an indefiniteness rejection as to the amount of crystalline material permitted, Glaxo acquiesced in the rejection and inserted the narrowing phrase "essentially free from crystalline material" from the dependent claim into the independent claim. JA 10-12, 34. Despite the

clear mandate of 35 U.S.C. § 112, ¶ 4, which requires dependent claims to be narrower than the independent claim from which they depend by containing an additional limitation, the district court concluded that Glaxo's amendment was not narrowing and proceeded to broadly construe the disputed claim limitation without regard for the surrender of subject matter necessary to obtain the patent. JA 37-38, 38 n.15.

5. The District Court's Grant Of A Preliminary Injunction

After construing the disputed limitation to mean "free of crystalline cefuroxime axetil that materially detracts from or affects the characteristics of the claimed invention," the district court then determined that the cefuroxime axetil antibiotic set forth in Ranbaxy's ANDA was "essentially free from crystalline material" because "the level of crystalline cefuroxime axetil in Ranbaxy's likely product does not materially affect the characteristics of the cefuroxime axetil, specifically its bioavailability."[3] JA 37-38, 40. The court based this determination on a statement in Ranbaxy's ANDA regarding the bioequivalence of its cefuroxime axetil antibiotic relative to Glaxo's Ceftin® product. JA 41-42. Thus, the district court

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[3] In seeming contradiction to this determination, the district court also found "this crystalline material is an active ingredient of the [Ranbaxy] product, delivering cefuroxime to the patient." JA 41.

compared the cefuroxime axetil antibiotic that is the subject of Ranbaxy's ANDA to Glaxo's commercial Ceftin® product to determine infringement. Under its claim construction, the district court concluded that Glaxo had demonstrated a likelihood of success in proving literal infringement. JA 23, 42.

While stating that it need not consider infringement under the doctrine of equivalents, the district court stated that "it most likely would have concluded that [Ranbaxy's antibiotic] would infringe the '181 patent under this doctrine as well." JA 42 n.17. The court concluded that prosecution history estoppel does not bar application of the doctrine of equivalents because "it does not appear that Glaxo's amendment satisfies the requirements for a 'narrowing amendment'" under *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabaushiki Co.*, --- F.3d ---, ---, 56 U.S.P.Q.2d 1865, 1868, 1887-90 (Fed. Cir. 2000) (*en banc*). JA 38 n.15.

The district court discussed the irreparable harm, the balance of hardships and the public interest factors in view of its determination of the likelihood of success factor. JA 42-43, 47-48, 49. Based upon its determination of the likelihood of success factor, and its determination of the

other three factors in view of the likelihood of success factor, the district court granted a preliminary injunction against Ranbaxy. JA 1-2, 50.

Even though done in connection with a preliminary injunction motion, the district court indicated that it had provided a final construction of Claim 1 so as to find infringement. The finality of the court's construction is evidenced by the court's statement in its Memorandum and Order to Show Cause directing the parties to address the issue of "whether the order should be made final, thereby obviating the need for a bond." JA 50.

III. SUMMARY OF THE ARGUMENT

The district court erred in construing the claim limitation "essentially free from crystalline material" by adopting a meaning far different from its ordinary meaning and unsupported by the intrinsic evidence. The ordinary meaning of "essentially free from crystalline material," consistent with the intrinsic evidence, is having fundamentally no crystalline material. Under the district court's erroneous construction, the cefuroxime axetil can have 15% or more crystalline material and still be "essentially free from crystalline material." To illustrate that the court's construction is totally at odds with the ordinary meaning, imagine a dieter's surprise to find a product labeled "essentially free from" sugar actually containing 15% or more sugar.

The district court attempted to support its erroneous claim construction by adopting Glaxo's proposal that "essentially free from" somehow means the same thing as the recognized transitional phrase "consisting essentially of." To the contrary, "essentially free from" is a negative limitation having no relationship to the transitional phrase "consisting essentially of."

The district court's claim construction also finds no support in the record, and indeed the district court cited to no intrinsic evidence for support in its entire opinion. The district court's construction contradicts the priority document in the '181 prosecution history, which specifically defines the disputed limitation as meaning that any amount of crystalline material present is "undetectable" and "may be assumed to be zero for all practical purposes." Moreover, the district court's construction contradicts Glaxo's own extrinsic evidence, which shows that crystalline cefuroxime axetil is detectable at 10%, and even at 5%.

The district court's construction also contradicts the salient portions of the written description and the prosecution history of the '181 patent, which magnify the error in the court's construction. The written description sets forth two embodiments: (1) a broad disclosure of cefuroxime axetil in

"substantially amorphous form," and (2) a preferred embodiment of the "substantially amorphous form" that is "essentially free from crystalline material." Example 22 is expressly directed to the broad, "substantially amorphous form," which Glaxo represented to the PTO as having 10% crystalline material. Other examples are directed to the narrow preferred embodiment, e.g., the "absence of crystals" (Example 1), the "presence of a few crystals" (Example 18) and "< 1% crystalline material" (Example 21).

Importantly, Glaxo attempted and failed to obtain a claim to the broad embodiment of cefuroxime axetil in "substantially amorphous form." Rather, in response to an indefiniteness rejection, Glaxo narrowed the claim by inserting the phrase "essentially free from crystalline material" from a dependent claim into an independent claim and cancelled the phrase "substantially amorphous form." Thus, Glaxo surrendered coverage of the broader embodiment. Accordingly, because "essentially free from crystalline material," originally present in a dependent claim, is narrower than the broad "substantially amorphous" embodiment, which Glaxo described as being able to have as much as 10% crystalline material, "essentially free from crystalline material" cannot be construed to cover 10% or more.

The ordinary meaning, the express definition in the priority document, the written description and the prosecution history show that "essentially free from crystalline material" should be construed to mean undetectable amounts of crystalline material (e.g., a few crystals or <1% crystalline material, as disclosed in the examples) that may assumed to be zero for all practical purposes. Glaxo's extrinsic evidence shows that crystalline cefuroxime axetil is detectable when present at 10%, and even at 5%. In no event, however, can the disputed limitation be construed to cover cefuroxime axetil in "substantially amorphous form," i.e., as much as 10% crystalline material, because this is the claim scope Glaxo surrendered to obtain its patent.

Therefore, Ranbaxy's cefuroxime axetil antibiotic, which undisputedly contains 10-15% crystalline material, is not "essentially free from crystalline material" and cannot literally infringe the '181 patent. Moreover, Glaxo's amendment during prosecution precludes any application of the doctrine of equivalents with respect to the "essentially free from crystalline material" limitation. Thus, Ranbaxy's cefuroxime axetil antibiotic also cannot infringe under the doctrine of equivalents.

Ranbaxy's antibiotic cannot infringe any claim of the '181 patent under the proper claim construction, and thus Glaxo cannot show any likelihood of success on the merits. Moreover, because the district court's discussion of the other three preliminary injunction factors was premised upon its erroneous assessment of likelihood of success, which it considered to be strong, the district court abused its discretion in granting the preliminary injunction.

IV. ARGUMENT

A. Standard of Review

This Court reviews questions of claim construction *de novo*. *See Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1454, 1456, 46 U.S.P.Q.2d 1169, 1172-73, 1174 (Fed. Cir. 1998) (*en banc)*; *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979, 34 U.S.P.Q.2d 1321, 1329 (Fed. Cir. 1995) (*en banc*), *aff'd*, 517 U.S. 370 (1996). This Court reviews decisions granting a preliminary injunction under an abuse of discretion standard. *See Novo Nordisk of N. Am., Inc. v. Genentech, Inc.*, 77 F.3d 1364, 1367, 37 U.S.P.Q.2d 1773, 1775 (Fed. Cir. 1996).

To overturn the grant of the preliminary injunction based on an abuse of discretion, Ranbaxy must show that the district court based its decision on

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IV. ARGUMENT

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Here, the district court erred by construing "essentially free from crystalline material" to permit the presence of any amount of crystalline material that does not "materially detract[] from or affect[] the characteristics of the claimed invention." JA 37-38. In so doing, the court adopted a claim construction contrary to the ordinary meaning of the language of the claim, contrary to the written description of the patent and contrary to the prosecution history of the patent. In struggling to adopt Glaxo's proffered claim construction, the district court went so far as to use extrinsic evidence to contradict an express definition of the disputed claim limitation found in the intrinsic evidence. JA 28-33.

1. "Essentially Free From Crystalline Material" Has An Ordinary Meaning

This Court has emphasized that the language of the claim frames and ultimately resolves all issues of claim interpretation. *See AbTox, Inc. v. Exitron Corp.*, 122 F.3d 1019, 1023, 43 U.S.P.Q.2d 1545, 1548, *amended by*, 131 F.3d 1009, 46 U.S.P.Q.2d 1735 (Fed. Cir. 1997). Claim 1 recites "[c]efuroxime axetil in amorphous form essentially free from crystalline material." JA 73 (emphasis added). The only contested limitation of this phrase is the meaning of "essentially free from crystalline material." JA 26.

Claim terms are given their ordinary meaning, unless it is clear from the written description or the prosecution history that the patentee expressly defined the claim term differently. *See K-2 Corp. v. Salomon S.A.*, 191 F.3d 1356, 1362-63, 52 U.S.P.Q.2d 1001, 1004 (Fed. Cir. 1999) (claim terms are given their ordinary meaning, but "a different meaning clearly and deliberately set forth in the intrinsic materials — the written description or the prosecution history — will control."); *Johnson Worldwide Assocs. v. Zebco Corp.*, 175 F.3d 985, 989, 50 U.S.P.Q.2d 1607, 1610 (Fed. Cir. 1999). In this case, neither the written description nor the prosecution history specifically defines the disputed limitation differently from its ordinary meaning. To the contrary, the intrinsic evidence sets forth an express definition of the disputed claim limitation that is consistent with the ordinary meaning.

The '181 patent recites that cefuroxime axetil exists in two distinct forms, the amorphous form and the crystalline form, and touts certain advantages of the amorphous form over the crystalline form. JA 67 (col. 2, ll. 1-22). The plain language of Claim 1, "[c]efuroxime axetil in amorphous form essentially free from crystalline material," refers to both physical forms, and requires the amorphous form to the virtual exclusion of the

crystalline form. The "essentially free from crystalline material" limitation is thus a negative limitation that excludes crystalline material in favor of amorphous material. *See In re Wakefield*, 422 F.2d 897, 904, 164 U.S.P.Q. 636, 641 (C.C.P.A. 1970) (approving the use of a negative limitation to exclude the prior art from the scope of a claim); Manual of Patent Examining Procedures § 2173.05(i) (7th ed. 2000) (approving the use of negative claim limitations to exclude subject matter from claims).

Given its plain meaning, "essentially free from crystalline material" means that the cefuroxime axetil contains virtually no crystalline material. One would expect a candy bar "essentially free from" fat to contain negligible fat, not 10-15% fat. One would expect a beverage "essentially free from" sugar to contain negligible sugar, not 10-15% sugar. The same is true of Claim 1. Cefuroxime axetil "essentially free from crystalline material" contains negligible crystalline cefuroxime axetil, certainly not 10-15% crystalline cefuroxime axetil.

In *In re Marosi*, 710 F.2d 799, 218 U.S.P.Q. 289 (Fed. Cir. 1983), this Court determined that the phrase "essentially free" does not permit the presence of the material at issue as an "essential ingredient[]," but only as an

"unavoidable impurit[y]."[4] *Id.* at 802-03, 218 U.S.P.Q. at 292. Under this definition, "essentially free from crystalline material" means that crystalline cefuroxime axetil may be present, if at all, only as an unavoidable impurity.

a. The District Court's "Ordinary Meaning" Is Contrary To The Language Of The Claim

The district court ascribed an "ordinary meaning" to the disputed claim limitation that ignores the actual words of the limitation and that adds meanings not present anywhere in the claim. Instead of giving "essentially free from crystalline material" its actual ordinary meaning, which restricts the amount of crystalline material, in sharp contrast, the district court opened the claim to permit unspecified and unknowable amounts of crystalline cefuroxime axetil. The district court construed the "essentially free from crystalline material" limitation not as meaning free from crystalline cefuroxime axetil, but only "free of crystalline cefuroxime axetil that materially detracts from or affects the characteristics of the claimed invention." JA 37-38. Thus, under the court's construction, there is no restriction on the amount of crystalline material, as long as it does not

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[4] The unrebutted evidence shows that the crystalline cefuroxime axetil in Ranbaxy's antibiotic "is an active ingredient," JA 15, 41, 673-74 (Ternyik Decl., ¶ 6), and thus an essential part of the drug product.

materially detract from or affect the characteristics of the claimed invention — whatever they may be. Obviously, this cannot be the ordinary meaning of the claim language.

In construing the disputed claim language, the district court improperly focused on the "functions and characteristics of the medication" — "specifically its bioavailability." JA 28, 40. Because the language of the claim does not, in any way, refer to "medication," "bioavailability" or any functional characteristics, the district court impermissibly added these words to the claim. JA 73 (Claim 1). Simply put, Claim 1 specifies a composition of matter and what that composition does not contain — more than a negligible amount of crystalline material.

The district court indicated that "essentially" is defined to mean "fundamentally" and "essential" is defined to mean "belonging to or being a part of the essence of something." JA 27. The essence or fundamental attribute of the composition of Claim 1 is that it is "free from crystalline material." This is consistent with the patent's teaching to use amorphous cefuroxime axetil to the exclusion of crystalline cefuroxime axetil. JA 67 (col. 2, ll. 20-22), 68 (col. 4, line 46) ("avoid formation of any crystalline material."). However, rather than adopting this ordinary meaning, the

district court determined that the dictionary definition of "essentially" required "an interpretation of the claim language as focusing on whether the crystalline material fundamentally affects the characteristics and functions of the cefuroxime axetil invention." JA 27. This construction opens the claim to unspecified and undetermined amounts of crystalline material, based on criteria that are not set forth in Claim 1 or in the patent. The district court's leap from the dictionary definition of "essentially" to this construction finds no support in the intrinsic evidence, let alone the words of the claim.

b. "Essentially Free From Crystalline Material" Is Not A Transitional Phrase

The district court's unsupported leap from the dictionary definition of "essentially" to the claim construction it adopted stems, in part, from Glaxo's novel position that "essentially free from" has the same meaning as the recognized transitional phrase "consisting essentially of." Glaxo represented to the district court that:

> The patent claim term "essentially free", and synonym expressions such as "consisting essentially of", "substantially", and the like have been repeatedly construed all to the same effect: that referenced material (here crystalline cefuroxime

axetil) is not totally excluded. Rather, it is excluded only in an amount which would materially affect "the characteristics of the invention".

JA 177; *see* JA 1500, 1503, 1707. Contrary to Glaxo's representation and the district court's adoption of Glaxo's construction, "essentially free from crystalline material" does not have the same meaning as the transitional phrase "consisting essentially of."

"Consisting essentially of" is a recognized transitional phrase that partially opens a claim. *See PPG Indus. v. Guardian Indus. Corp.*, 156 F.3d 1351, 1354, 48 U.S.P.Q.2d 1351, 1353 (Fed. Cir. 1998). This transitional phrase permits the inclusion of materials other than those specified in the claim, so long as the additional materials do not affect the basic and novel properties of the claimed subject matter. *See id.*, 48 U.S.P.Q.2d at 1353-54; *Water Techs. Corp. v. Calco, Ltd.*, 850 F.2d 660, 666, 7 U.S.P.Q.2d 1097, 1102 (Fed. Cir. 1988). On the other hand, "essentially free from" is not a recognized transitional phrase, nor is it used as a transitional phrase in Claim 1 of the '181 patent. In fact, Claim 1 of the '181 patent does not contain any recognized transitional phrase. Rather, "essentially free from crystalline material" is used as a negative limitation in Claim 1, specifying what is not

included in the claimed subject matter — more than a negligible amount of crystalline material. *See In re Wakefield*, 422 F.2d at 904, 164 U.S.P.Q. at 641; Manual of Patent Examining Procedures § 2173.05(i).

Thus, while "consisting essentially of" partially opens a claim, "essentially free from" closes Claim 1 by restricting the amount of crystalline material. The district court, in essence, rewrote Claim 1 to read "a medication consisting essentially of cefuroxime axetil in substantially amorphous form." This is not, however, what the claim says. Even if it were, more than negligible amounts of crystalline material would still not be covered because restricting the amount of crystalline material was the goal of the invention. JA 67 (col. 2, ll. 1-9).

As discussed in detail below, Glaxo attempted to obtain a claim which read "cefuroxime axetil in highly pure, substantially amorphous form." However, in response to a rejection, Glaxo cancelled this claim and forever surrendered its coverage. In short, the district court erred in giving the disputed claim limitation a meaning other than its ordinary meaning, which would provide Glaxo with claim scope far greater than the broad claim Glaxo cancelled during prosecution.

2. "Essentially Free From Crystalline Material" Is Expressly Defined In The Intrinsic Evidence

When a claim limitation is expressly and clearly defined in the written description or the prosecution history of a patent, the patentee's express definition prevails over the ordinary meaning. *See K-2*, 191 F.3d at 1362-63, 52 U.S.P.Q.2d at 1004, *Johnson*, 175 F.3d at 989, 50 U.S.P.Q.2d at 1610. Here, Glaxo expressly defined "essentially free from crystalline material" in the priority document in the prosecution history of the '181 patent. Glaxo's express definition fully accords with the ordinary meaning of this limitation.

The '181 patent claims priority to United Kingdom Patent Application No. 8222019. JA 64. During prosecution of the '181 patent, Glaxo submitted a certified copy of the UK application as part of its claim of priority. JA 790-98. The UK application recites:

> The cefuroxime 1-acetoxyethyl ester in accordance with the invention is preferably essentially free from crystalline material, by which we mean that any amount of crystalline material which may be present is so low as to be undetectable by X-ray crystallography, i.e. that an X-ray photograph of a

> sample of the compound shows no rings. The crystalline content of such a sample may be assumed to be zero for all practical purposes.

JA 797 (emphases added); *see* JA 841-55 (complete priority document). Thus, Glaxo expressly defined "essentially free from crystalline material" to mean that any amount of crystalline cefuroxime axetil present is undetectable.

Inexplicably, the district court found that "[t]his definition does not overcome the ordinary and reasonable interpretation of the [disputed claim] phrase." JA 28. Contrary to the district court's conclusion, however, Glaxo's express definition is indeed completely consistent with and confirms the correct ordinary meaning of the disputed claim limitation. Moreover, Glaxo's express definition accords with the only precedent construing "essentially free." *See In re Marosi*, 710 F.2d at 802-03, 218 U.S.P.Q. at 292 (construing "essentially free" to include only undetectable quantities of the material at issue). Given this consistency, the district court erred in rejecting Glaxo's express definition of "essentially free from crystalline material."

The district court also attempted to avoid Glaxo's express definition because it "is not contained in the '181 patent application or other parts of the patent history, but only in a 1982 foreign application about which we know very little." JA 30. The district court's rejection of the definition on this basis fails as contrary to law.

Glaxo was required to and did make the UK application part of the prosecution history of the '181 patent in order to establish its claim of priority. JA 790-98; *see* 35 U.S.C. § 119(b). While jettisoning the express definition in the priority document, the district court did recognize that in making the claim of priority the UK application became part of the prosecution history of the '181 patent, "and therefore a part of the intrinsic evidence available for claim construction." JA 28-30. This statement contradicts the district court's stated basis for rejecting the definition in the priority document and correctly recognizes that the definition in the priority document is part of the prosecution history that must be used to interpret the claims.

Under 35 U.S.C. § 119(a), a later-filed United States patent application enjoys the benefit of the filing date of an earlier-filed foreign patent application "for the same invention." Thus, Glaxo could only claim

the benefit of the filing date of the earlier-filed UK application if the later-filed United States application was for the "same invention." 35 U.S.C. § 119(a). Since the '181 patent uses the phrase "essentially free from crystalline material" and is for the same invention as the UK application, this phrase must be given the same meaning in the '181 patent as that expressly ascribed to it by Glaxo in the UK application. *See Augustine Med., Inc. v. Gaymar Indus., Inc.*, 181 F.3d 1291, 1300, 50 U.S.P.Q.2d 1900, 1907 (Fed. Cir. 1999) ("the prosecution history of a parent application may limit the scope of a later application using the same claim term."); *Tanabe Seiyaku Co. v. United States Int'l Trade Comm'n*, 109 F.3d 726, 733, 41 U.S.P.Q.2d 1976, 1982-83 (Fed. Cir. 1997) (looking to statements made during prosecution of related foreign patent applications); *Jonsson v. Stanley Works*, 903 F.2d 812, 818, 14 U.S.P.Q.2d 1863, 1869 (Fed. Cir. 1990) (using the prosecution history of related applications using the same claim term to construe the claim term); *Caterpillar Tractor Co. v. Berco S.p.A.*, 714 F.2d 1110, 1116, 219 U.S.P.Q. 185, 188 (Fed. Cir. 1983); *Evans Med. Ltd. v. American Cyanamid Co.*, 11 F. Supp. 2d 338, 355 (S.D.N.Y. 1998), *aff'd*, 215 F.3d 1347 (Fed. Cir. 1999) (unpublished) (using the UK patent application from which the later United States patent claimed priority to

construe a disputed claim term). If Glaxo had wished to disavow the express definition in its priority document, it was incumbent on Glaxo to make such disavowal on the public record in the Patent Office. The public record reflects no such disavowal.

As such, "essentially free from crystalline material" means containing only "undetectable" amounts of crystalline material, i.e., amounts that are "zero for all practical purposes." JA 797, 845.

3. The District Court Improperly Used Extrinsic Evidence To Avoid Glaxo's Express Definition

Faced with its own narrow definition in the prosecution history, Glaxo attempted to avoid this definition using extrinsic evidence — a declaration from one of its employees and four exhibits comprising X-ray photographs (Exhibits A-C) and a November 3, 1983 internal Glaxo report entitled "Methods of detection of crystalline material in amorphous E47 ester and characterization of its diastereoisomeric polymorphs" (Exhibit D). JA 1638-42 (declaration), 1643-84 (Exhibits A-D). The district court accepted and relied upon this extrinsic evidence, despite the court's acknowledgement that "[a] court commits error if it uses extrinsic evidence, such as expert testimony, unless the intrinsic evidence is insufficient." JA 24, 31-33.

Moreover, this extrinsic evidence is completely consistent with the express definition set forth during prosecution of the '181 patent and with the ordinary meaning of the disputed claim limitation.

The declaration and the four exhibits were not before the Patent Office nor are they part of the public record of the '181 patent. Thus, Glaxo cannot use this extrinsic evidence to disavow the express definition of "essentially free from crystalline material" contained in the intrinsic evidence in favor of a broader, litigation-driven claim interpretation. *See Vitronics*, 90 F.3d at 1583-84, 39 U.S.P.Q.2d at 1577-78 (expert testimony inconsistent with the intrinsic evidence should be accorded no weight because competitors are entitled to rely on the public record to ascertain the scope of a claim); *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1308, 51 U.S.P.Q.2d 1161, 1168 (Fed. Cir. 1999) (courts should not rely on extrinsic evidence in claim construction to contradict the meaning of claims discernible from thoughtful examination of the intrinsic evidence); *Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1576, 34 U.S.P.Q.2d 1673, 1677 (Fed. Cir. 1995) ("Claims may not be construed one way in order to obtain their allowance and in a different way against accused infringers."); *Lemelson v. General Mills, Inc.*, 968 F.2d 1202, 1208, 23

U.S.P.Q.2d 1284, 1289 (Fed. Cir. 1992) ("Other players in the marketplace are entitled to rely on the record made in the Patent Office in determining the meaning and scope of the patent.").

Glaxo's employee, Robert Lancaster, first opines regarding Debye-Scherrer (a type of X-ray analysis) photographs taken by "scientists at Glaxo" in 1982-83. JA 1640 (Lancaster Decl., ¶ 3), 1645 (Exhibit C showing photographs). Lancaster's seventeen-year after-the-fact opinion is that with "reasonably good sample preparation and film processing" the detection level of crystalline cefuroxime axetil is "about 10-15%." JA 1640 (Lancaster Decl., ¶ 7). However, the district court acknowledged, based on its own observation of the photographs, that "the lines do appear more distinct in the pictures of samples containing a greater proportion of crystalline material." JA 31. By referring to "pictures" in the plural, the court must have been referring to the photographs showing 10% and 15% crystalline material. *Id.*; JA 1645 (Exhibit C containing three photographs of 5%, 10% and 15% crystalline material). Thus, the photographs support the proposition that the detection level is at least as low as 10%.

The court and Lancaster next turned to the 1983 Glaxo report. The court acknowledged that the report "indicated that the smallest amount of

crystalline material detectable was 10%." JA 32, 1652 (Glaxo report, Table I). Lancaster concurred and thus contradicted his own declaration:

> This report also concluded that detection levels of crystalline cefuroxime axetil by Debye-Scherrer X-ray photography was about 10%.

JA 1641 (Lancaster Decl., ¶ 8).

Moreover, as the district court acknowledged, the report, in fact, supports detection levels even lower than 10%. JA 32 n.9. The report expressly states that "Isomer A (II) was visible at the 5% level." JA 1650. Table II of the report shows that 5-10% crystalline material was detectable by X-ray photography in sample JSC 3726C. JA 1653.

In the UK application, Glaxo expressly defined "essentially free from crystalline material" to mean containing only "undetectable" amounts of crystalline material. JA 797, 845. Even accepting Glaxo's own extrinsic evidence, crystalline cefuroxime axetil was clearly detectable at 10% and even as low as 5%. JA 1650, 1652-53. Thus, even based on this extrinsic evidence, "essentially free from crystalline material" must contain less than 5% crystalline material, and cannot possibly contain 10% crystalline material.

Despite finding that "the United Kingdom patent definition does perhaps favor a more restrictive interpretation of the claim," the district court accepted Lancaster's opinion about the photographs in Exhibit C, while ignoring his statement about the report, in order to avoid the express definition contained in the priority document. JA 32-33. The district court thus erroneously concluded that:

> The X-ray test's inability to detect crystalline material below 10%, and possibly even 15% in some cases, indicates that, in the words of the United Kingdom patent, "zero for all practical purposes" is actually a number just below 10% and perhaps even just below 15%.[5]

JA 33 (footnote added).

The only support for the district court's claim construction is the unsupported opinion of Glaxo's employee, who in the very same declaration

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[5] Error in the district court's claim construction also manifests from the fact that the court's construction permits crystalline material in levels at least as high as 20%, if not higher. JA 1054 (Ranbaxy's ANDA states that "it can be conclusively stated that the formulation with the crystalline component, even up to 20%, is bioequivalent to Ceftin® tablets."). Thus, according to the court's construction, 20% crystalline material must also be "undetectable," which is clearly incorrect.

contradicts his 10-15% detection limit.[6] The 10-15% detection limit, which comes only from Lancaster and not from any exhibit of record, is a litigation-contrived limit based on Ranbaxy's accused antibiotic. There is no support whatsoever for concluding that 10% crystalline material, let alone 15% or more, was undetectable. *See Desper Prods., Inc. v. QSound Labs., Inc.*, 157 F.3d 1325, 1340, 48 U.S.P.Q.2d 1088, 1099 (Fed. Cir. 1998) ("[p]ost-hoc, litigation-inspired argument cannot be used to reclaim subject matter that the public record in the PTO clearly shows has been abandoned.").

The intrinsic evidence does not support the district court's conclusion, and Glaxo's own contemporaneous extrinsic evidence shows that 5% crystalline material was detectable. JA 1650, 1653. Thus, the district court's reliance upon and interpretation of the extrinsic evidence submitted by Glaxo were erroneous.

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[6] While seizing on Lancaster's unsupported opinion of 10-15%, the district court did not construe Claim 1 to mean 10-15% crystalline material. It could not do so because such a range is flatly contradicted by the written description and prosecution history of the '181 patent, as discussed in detail below.

4. The Written Description Of The '181 Patent Supports The Ordinary Meaning And The Express Definition Of "Essentially Free From Crystalline Material"

Surprisingly, the district court determined that the written description of the '181 patent, including the examples, did not aid in the construction of the "essentially free from crystalline material" limitation. JA 35-36. The court found that "[g]iven the context of this case, these examples cannot be used to create any distinction because of the inherent confusion and lack of clarity involved." JA 36. Contrary to the district court's conclusion, however, the written description of the '181 patent does aid in construing the disputed limitation.

The written description of the '181 patent discloses two embodiments: (1) cefuroxime axetil "in highly pure, substantially amorphous form" and (2) a preferred subset of the "substantially amorphous form" which is "essentially free from crystalline material." JA 67 (col. 2, ll. 23-40); 69 (col. 6, ll. 7-10). The written description recites:

> According to one aspect of the present invention, there is provided cefuroxime axetil in highly pure, substantially amorphous form.

. . .

> The cefuroxime axetil ester in accordance with the present invention is preferably essentially free from crystalline material.

JA 67 (col. 2, ll. 23-40) (emphases added). The written description expressly states that cefuroxime axetil "essentially free from crystalline material" is the "preferred embodiment." JA 69 (col. 6, ll. 7-10).

The examples of the patent illuminate this distinction. Example 26 of the patent recites "substantially amorphous" cefuroxime axetil. JA 72 (col. 11, ll. 39-40). Example 22 of the patent likewise recites that "X-ray crystallography revealed the product was substantially amorphous." JA 71 (col. 10, ll. 26-28) (emphasis added). Moreover, during prosecution of two process patents relating to cefuroxime axetil, both of which claim priority to the same UK application as the '181 patent, Glaxo represented to the Patent Office on two different occasions that the identical Example 22 shows cefuroxime axetil having "a small content of crystalline material, estimated at about 10%" and as containing "approximately 10% crystalline material." JA 1230, 1244; *see* JA 71, 1218, 1225, 1232, 1239; *see also Jonsson*, 903 F.2d at 818, 14 U.S.P.Q.2d at 1869 (construing the same term in two patents

stemming from the same parent application the same way); *Elkay Mfg. Co. v. Ebco Mfg. Co.*, 192 F.3d 973, 980, 52 U.S.P.Q.2d 1109, 1114 (Fed. Cir. 1999). Thus, these examples show that the broader embodiment of "substantially amorphous" cefuroxime axetil refers to cefuroxime axetil that contains as much as 10% crystalline material.

The preferred subset of cefuroxime axetil "essentially free from crystalline material" must therefore contain less crystalline material, i.e., less than 10%. While none of the examples expressly recites cefuroxime axetil "essentially free from crystalline material," Example 1 describes cefuroxime axetil that when subjected to Debye-Scherrer X-ray powder analysis "gave a plain halo (absence of crystals, confirming the amorphous nature of the product)." JA 70 (col. 8, ll. 9-10) (emphasis added). Example 18 discloses cefuroxime axetil that showed "a few faint lines" when subjected to X-ray powder analysis, suggesting "the presence of a few crystals." JA 71 (col. 9, ll. 29-30) (emphasis added). Example 21 discloses cefuroxime axetil that contained "≤1% crystalline material" upon microscopic examination. *Id.* (col. 10, ll. 4-5) (emphasis added). Since these are the only examples addressing the level of crystalline material, other than those specifically identified as showing "substantially amorphous" cefuroxime axetil, these

examples obviously refer to the narrow subset of cefuroxime axetil which is "essentially free from crystalline material."

Thus, the patent examples show that the narrow subset of cefuroxime axetil which is "essentially free from crystalline material" is cefuroxime axetil containing "a few crystals" or "<1% crystalline material." This disclosure is consistent with the ordinary meaning of the disputed claim limitation. These examples are also consistent with the express definition set forth in the prosecution history. Glaxo expressly defined "essentially free from crystalline material" to mean that "any amount of crystalline material which may be present is so low as to be undetectable," and Glaxo's extrinsic evidence shows that 10% and even 5% crystalline material is detectable. JA 797, 845, 1650, 1652-53. Thus, the examples, which show "a few crystals" or "<1% crystalline material," represent cefuroxime axetil "essentially free from crystalline material."

5. The Prosecution History Shows That Glaxo Surrendered Claim Coverage For The Broader Embodiment Disclosed In The Written Description

The prosecution history of the '181 patent shows that Glaxo attempted to obtain coverage for the broader disclosed embodiment — cefuroxime

axetil in "substantially amorphous form." However, during prosecution, Glaxo was forced to surrender coverage of this embodiment in order to obtain the patent. Thus, Glaxo had to settle for claim coverage of the narrower preferred embodiment — cefuroxime axetil "essentially free from crystalline material."

As originally filed, the application that issued as the '181 patent claimed:

> 1. Cefuroxime axetil in highly pure, substantially amorphous form.
>
> . . .
>
> 4. The product of claim 1 essentially free from crystalline material.

JA 728 (emphases added). Because dependent claims are required by statute to be narrower than the independent claim from which they depend, cefuroxime axetil "essentially free from crystalline material" is necessarily a narrower subset of cefuroxime axetil in "substantially amorphous form." *See* 35 U.S.C. § 112, ¶ 4. Thus, cefuroxime axetil "essentially free from crystalline material" must contain less crystalline material than cefuroxime axetil in "substantially amorphous form," which Glaxo admitted is as much

as 10%. JA 71, 1218, 1225, 1230, 1232, 1239, 1244. Thus, given its broadest construction, "essentially free from crystalline material" certainly must mean containing less than 10% crystalline material.

The patent Examiner rejected originally-filed Claims 1 and 4 as indefinite and as obvious over Glaxo's earlier '320 patent:

> Claims 1-9 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.
>
> It is not definite what is particularly included or excluded by the term "highly pure, substantially amorphous form". It is noted that there is no particular limit indicated for the amounts of impurities while applicants do not regard residual solvents as impurities (page 3, lines 24-36). It is also not clear how much crystalline material is permitted. Dependent claim 4 specifies a product which is essentially free from crystalline material. . . .
>
> Claims 1-9 are rejected under 35 U.S.C. § 103 as being unpatentable over Gregson et al. [Glaxo's '320 patent].

JA 785-87 (emphasis added). The patent Examiner's indefiniteness rejection had two components: (1) the level of crystalline material permitted by the claims was not clear and (2) the level of impurities permitted by the claims was not clear.

The indefiniteness rejection regarding the level of crystalline material was made against the phrase "substantially amorphous form." In the rejection, the patent Examiner even suggested that the phrase in Claim 4 "essentially free from crystalline material," unlike the phrase "substantially amorphous form" in Claim 1, makes it clear ("specifies") how much crystalline material is permitted.[7]

Glaxo responded to the Examiner's rejections by canceling Claims 1 and 4. JA 801-02. Glaxo replaced these claims with a claim limited to cefuroxime axetil "essentially free from crystalline material." JA 801 (added independent Claim 10). This claim ultimately issued as Claim 1 of the '181 patent after further amendments not relevant here. *Compare id.* (added Claim 10) *to* JA 73 ('181 patent, Claim 1). Glaxo admits that it

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[7] The patent Examiner properly rejected Claim 1 and all its dependent claims, including Claim 4, as indefinite because the dependent claims by definition include all the language of independent Claim 1, i.e., "substantially amorphous form." *See* 35 U.S.C. § 112, ¶ 4.

amended the phrase "substantially amorphous form" to "essentially free from crystalline material" to overcome the indefiniteness rejection regarding the permissible level of crystalline material. JA 176 n.14.

In amending the claims with respect to the level of crystalline material, Glaxo surrendered patent coverage for cefuroxime axetil "in highly pure, substantially amorphous form" as disclosed in Example 22, containing approximately 10% crystalline material, and Example 26. *See Novo Nordisk*, 77 F.3d at 1369, 37 U.S.P.Q.2d at 1777-78 (noting that the claims, "not the specification, measure the protected patent right" and that "all that appears in the specification is not necessarily within the scope of the claims," and finding that an embodiment disclosed in the specification was not covered by the claims). Glaxo narrowed its claims to cover cefuroxime axetil "essentially free from crystalline material" as disclosed in Examples 1, 18 and 21, which disclose cefuroxime axetil with no crystals, "a few crystals" and "<1% crystalline material," respectively. Glaxo cannot now recover the claim scope it surrendered in order to obtain the '181 patent. *See Southwall*, 54 F.3d at 1576, 34 U.S.P.Q.2d at 1676 ("The prosecution history limits the interpretation of claim terms so as to exclude any interpretation that was disclaimed during prosecution.").

The district court dismissed the significance of the prosecution history by stating that "[t]he rejection was based on indefiniteness grounds and not an express concern that the application language claimed excessive percentages of crystalline cefuroxime axetil." JA 34. The court's view fails to recognize that under 35 U.S.C. § 112, ¶ 4, "essentially free from crystalline material" is narrower than cefuroxime axetil in "substantially amorphous form" because the former was present in a dependent claim. The district court's misunderstanding of the prosecution history is confirmed by its statement that Glaxo's amendment was not a narrowing amendment and its apparent reliance on the fact that the phrase "essentially free from crystalline material" was never amended. JA 34, 38 n.15. By definition, when Glaxo incorporated the "essentially free from crystalline material" limitation from a dependent claim into an independent claim, it narrowed the scope of the independent claim.

As defined by Glaxo, "essentially free from crystalline material" means cefuroxime axetil in which any amount of crystalline material is undetectable. JA 797, 845. The intrinsic evidence shows that this means containing only "a few crystals" or "<1% crystalline material." JA 70-71. The extrinsic evidence confirms this claim construction by showing that 5%

crystalline material is detectable. JA 1650, 1653. In no case can this claim limitation be construed to encompass cefuroxime axetil containing 10% crystalline material, because that is exactly the claim scope Glaxo surrendered to obtain the '181 patent.

C. The District Court Erred In Assessing Likelihood Of Success

1. Ranbaxy's Cefuroxime Axetil Antibiotic Does Not Literally Infringe The Properly Construed Claims Of The '181 Patent

a. The District Court Erroneously Compared Ranbaxy's ANDA To Glaxo's Commercial Ceftin® Product

By erroneously construing "essentially free from crystalline material" to mean "free from crystalline cefuroxime axetil that materially detracts from or affects the characteristics of the claimed invention," the district court left itself no standard by which to assess infringement. JA 37-38. The '181 patent does not provide any basis for assessing the functional characteristics of "cefuroxime axetil in amorphous form essentially free from crystalline material" because the patent only describes and claims a composition. Left with no standard by which to assess infringement, the district court impermissibly compared the cefuroxime axetil antibiotic set

forth in Ranbaxy's ANDA to Glaxo's commercial embodiment of the '181 patent, Ceftin®, rather than to Claim 1 of the patent. JA 41, 1199 (showing that Glaxo marks its Ceftin® product with the '181 patent number).

The district court concluded that "the level of crystalline cefuroxime axetil in Ranbaxy's likely product does not materially affect the characteristics of the cefuroxime axetil, specifically its bioavailability." JA 40. In reaching this conclusion, the district court did not refer to any standard for bioavailability in the patent, and, in fact, the patent contains no such standard. Rather, the district court based its conclusion upon a statement in Ranbaxy's ANDA that Ranbaxy's cefuroxime axetil antibiotic "complies with the bioequivalence criteria." JA 41 (quoting from Ranbaxy's ANDA). This statement means that the drug product described in Ranbaxy's ANDA is bioequivalent to Glaxo's Ceftin® product; the statement has no bearing on whether Ranbaxy's product meets the limitations of Claim 1. Thus, the district court compounded its claim construction error by comparing Ranbaxy's ANDA to Glaxo's commercial embodiment rather than to Claim 1 of the '181 patent. *See Zenith Labs., Inc. v. Bristol-Myers Squibb Co.*, 19 F.3d 1418, 1423, 30 U.S.P.Q.2d 1285, 1289 (Fed. Cir. 1994) ("As we have repeatedly said, it is error for a court to compare in its

infringement analysis the accused product or process with the patentee's commercial embodiment or other version of the product or process; the only proper comparison is with the claims of the patent.").

Under the district court's claim construction and infringement analysis, it is not possible to make a cefuroxime axetil antibiotic that would satisfy the ANDA bioequivalence criteria without infringing the '181 patent, even though cefuroxime axetil is now in the public domain. In order to obtain FDA approval, the drug product set forth in the ANDA must be bioequivalent to an already-approved drug. JA 673 (Ternyik Decl., ¶ 4). In this case, Glaxo's Ceftin® product is the only approved drug, because Glaxo's '320 patent on cefuroxime axetil did not expire until May, 2000. JA 856, 868. Bioequivalence to Ceftin® means infringement of the '181 patent under the district court's claim construction, regardless of the amount of crystalline material. This cannot be correct, because it would encompass compositions containing 10%, 20%, 30%, 40%, etc. crystalline cefuroxime axetil. Ranbaxy's ANDA reports that percentages as great as 20% crystalline material had no adverse impact on the drug. JA 1054. Such compositions are obviously not "essentially free from crystalline material."

The results which flow from the district court's infringement analysis confirm its legal error.

b. Ranbaxy's Cefuroxime Axetil Antibiotic Is Not "Essentially Free From Crystalline Material"

It is undisputed that the cefuroxime axetil antibiotic set forth in Ranbaxy's ANDA contains between 10-15% crystalline cefuroxime axetil. JA 15, 41, 673 (Ternyik Decl., ¶ 5), 895-97, 927-31, 1047, 1054. The proposed drug product contains 12% crystalline cefuroxime axetil and 88% amorphous cefuroxime axetil. JA 15, 41, 673 (Ternyik Decl., ¶ 5), 1035, 1054. Because "essentially free from crystalline material" is properly construed to mean containing only a few crystals or less than 1% crystalline cefuroxime axetil, the antibiotic set forth in Ranbaxy's ANDA does not literally infringe Claim 1 of the '181 patent because the antibiotic is not "essentially free from crystalline material." *See Strattec Sec. Corp. v. General Auto. Specialty Co.*, 126 F.3d 1411, 1418, 44 U.S.P.Q.2d 1030, 1036 (Fed. Cir. 1997). Since all other claims depend from Claim 1, Ranbaxy's antibiotic does not infringe any claim of the '181 patent. *See Wahpeton Canvas Co. v. Frontier, Inc.*, 870 F.2d 1546, 1553, 10 U.S.P.Q.2d 1201, 1208 (Fed. Cir. 1989) ("It is axiomatic that dependent claims cannot

be found infringed unless the claims from which they depend have been found to have been infringed.").

Even if "essentially free from crystalline material" were given a much broader construction to mean containing less than 10% crystalline material, the antibiotic set forth in Ranbaxy's ANDA would still not literally infringe Claim 1 of the '181 patent. There is no dispute that the level of crystalline cefuroxime axetil in the antibiotic set forth in Ranbaxy's ANDA is detectable. JA 1047, 1073-78. Under the ANDA, Ranbaxy is required to measure the amount of crystalline cefuroxime axetil to confirm it is between 10-15%. *Id.* This detectable amount of crystalline cefuroxime axetil would not satisfy the "essentially free from crystalline material" limitation, even if it were broadened to mean less than 10%.

Ranbaxy's antibiotic is the antithesis of "essentially free from crystalline material." The uncontroverted evidence shows that the crystalline cefuroxime axetil in Ranbaxy's ANDA formulation is not an inert material. JA 15, 41, 673-74 (Ternyik Decl., ¶ 6). Ironically, the district court found that the crystalline cefuroxime axetil in Ranbaxy's antibiotic "is an active ingredient of the product, delivering cefuroxime to the patient." JA 41. Thus, the crystalline cefuroxime axetil does materially affect the

composition by delivering the active moiety cefuroxime to the patient. JA 15, 41, 673-74 (Ternyik Decl., ¶ 6). As such, Ranbaxy's antibiotic does not infringe even under the district court's construction. Simply put, while Claim 1 of the '181 patent seeks to eliminate crystalline cefuroxime axetil, Ranbaxy's antibiotic specifically includes crystalline cefuroxime axetil as an active part of the drug product.

2. Ranbaxy's Cefuroxime Axetil Antibiotic Cannot Infringe The Claims Of The '181 Patent Under The Doctrine Of Equivalents

a. Prosecution History Estoppel Completely Bars Application Of The Doctrine Of Equivalents

The district court stated that it did "not have to consider whether Ranbaxy's likely product infringes the '181 patent under the doctrine of equivalents." JA 42 n.17. However, the court noted that it would likely have found infringement if having addressed this issue. *Id.* Contrary to the district court's conclusion, the doctrine of equivalents is not available to Glaxo because prosecution history estoppel completely bars equivalence.

As previously set forth, Glaxo's originally-filed patent claims recited:

1. Cefuroxime axetil in highly pure, substantially amorphous form.

4. The product of claim 1 essentially free from crystalline material.

JA 728 (emphases added). In response to the patent Examiner's indefiniteness rejection, Glaxo incorporated the "essentially free from crystalline material" limitation into the claim that issued as Claim 1 of the '181 patent. JA 785-87, 801-02. Glaxo cannot now challenge the necessity of this amendment. *See Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1356, 48 U.S.P.Q.2d 1674, 1678-79 (Fed. Cir. 1998).

Prosecution history estoppel is a question of law. *See Pharmacia & Upjohn Co. v. Mylan Pharms., Inc.*, 170 F.3d 1373, 1376, 50 U.S.P.Q.2d 1033, 1036 (Fed. Cir. 1999). This Court has determined that "a narrowing amendment made for any reason related to the statutory requirements for a patent will give rise to prosecution history estoppel with respect to the amended claim element." *Festo Corp. v. Shoketsu Kinzoku Kabushiki Co.*, --- F.3d ---, ---, 56 U.S.P.Q.2d 1865, 1870 (Fed. Cir. 2000) (*en banc*). The definiteness requirement of 35 U.S.C. § 112, ¶ 2 is one such statutory

requirement. *See id.* at 1870-71. "When a claim amendment creates prosecution history estoppel with regard to a claim element, there is no range of equivalents available for the amended claim element. Application of the doctrine of equivalents to the claim element is completely barred (a 'complete bar')." *Id.* at 1872.

The district court's sole comment regarding Ranbaxy's prosecution history estoppel argument was that "it does not appear that Glaxo's amendment satisfies the requirements for a 'narrowing amendment,' which the Festo Corp. court held precludes the application of the doctrine of equivalents." JA 38 n.15. The district court's conclusion is contrary to law. By amending the independent claim to incorporate the "essentially free from crystalline material" limitation present in dependent Claim 4, Glaxo necessarily narrowed the scope of the independent claim.[8] *See* 35 U.S.C. § 112, ¶ 4. This narrowing amendment creates prosecution history estoppel that completely bars application of the doctrine of equivalents as to the

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[8] The fact that Glaxo introduced the "essentially free from crystalline material" limitation into an independent claim by adding a new claim rather than amending originally-filed Claim 1 does not change the narrowing effect of Glaxo's amendment. JA 801-02 (showing that Glaxo added the limitation into new independent Claim 10 and cancelled Claims 1 and 4); *see Festo*, --- F.3d at ---, 56 U.S.P.Q.2d at 1887.

"essentially free from crystalline material" limitation. *See Festo*, --- F.3d at ---, 56 U.S.P.Q.2d at 1870, 1872. Thus, prosecution history estoppel completely bars any scope of equivalence, whatsoever, with respect to the "essentially free from crystalline material" limitation. The cefuroxime axetil antibiotic set forth in Ranbaxy's ANDA cannot infringe any claim of the '181 patent under the doctrine of equivalents as a matter of law.

b. Ranbaxy's Cefuroxime Axetil Antibiotic Is Substantially Different From The Claims Of The '181 Patent

Without analysis, the district court stated that "it most likely would have concluded" that Ranbaxy's antibiotic would infringe the '181 patent under the doctrine of equivalents. JA 42 n.17. The district court's conclusion is contrary to law and unsupported by the facts.

The doctrine of equivalents "is not allowed such broad play as to effectively eliminate" a claim limitation. *Warner Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 29, 117 S. Ct. 1040, 1049, 137 L. Ed. 2d 146 (1997); *see Sage Prods., Inc. v. Devon Indus., Inc.*, 126 F.3d 1420, 1424-26, 1429-30, 44 U.S.P.Q.2d 1103, 1106-08, 1110-11 (Fed. Cir. 1997). Finding the antibiotic of Ranbaxy's ANDA equivalent to the composition of Claim 1

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Ranbaxy's cefuroxime axetil antibiotic is not equivalent to Claim 1 of the '151 patent because the differences are substantial. *See Ethicon Endo-Surgery, Inc. v. United States Surgical Corp.*, 149 F.3d 1309, 1315, 47 U.S.P.Q.2d 1272, 1276 (Fed. Cir. 1998) (equivalence assessed on the basis of insubstantial differences); *but see Genentech, Inc. v. Wellcome Found. Ltd.*, 29 F.3d 1555, 1570, 31 U.S.P.Q.2d 1161, 1173 (Fed. Cir. 1994) (J. Lourie concurring) (explaining the inadequacy of the function, way, result test for evaluating equivalence between chemical compositions). Claim 1 requires cefuroxime axetil "essentially free from crystalline material" which Glaxo expressly defined as cefuroxime axetil with a crystalline content so low that it cannot be detected. JA 73, 797, 845. Glaxo also stated in its priority document that "[t]he presence of crystalline material . . . is preferably avoided." JA 797, 845. Ranbaxy's cefuroxime axetil antibiotic is the antithesis of "essentially free from crystalline material"

Ranbaxy's antibiotic, 10-15% crystalline cefuroxime axetil is present as an active component. JA 15, 41, 673-74 (Ternyik Decl., ¶¶ 5-6),

895-97, 927-31, 1047, 1054. This use of crystalline cefuroxime axetil as an active component is substantially different from attempting to eliminate crystalline material, i.e., having only undetectable amounts of crystalline cefuroxime axetil present. Simply put, Claim 1 seeks to eliminate the presence of crystalline cefuroxime axetil, while Ranbaxy's ANDA requires Ranbaxy to ensure the presence of crystalline material in the detectable amount of 10-15%. JA 1047, 1073-78. This difference in the amount of crystalline cefuroxime axetil is a substantial difference, i.e., a difference in kind, and precludes infringement under the doctrine of equivalents. *See Ethicon*, 149 F.3d at 1318-19, 1321, 47 U.S.P.Q.2d at 1278-79, 1280 (substantial difference is a "difference in kind").

Because Ranbaxy's cefuroxime axetil antibiotic does not infringe Claim 1 of the '181 patent either literally or under the doctrine of equivalents, the district court clearly erred in finding a likelihood of success on the merits. In turn, the district court abused its discretion in granting a preliminary injunction based on this erroneous finding. *See Novo Nordisk*, 77 F.3d at 1371, 37 U.S.P.Q.2d at 1779.

D. The District Court's Erroneous Determination Of The Likelihood Of Success Factor Infected Its Determination Of The Other Preliminary Injunction Factors

1. The District Court's Conclusion On Irreparable Harm Was Premised On Its Erroneous Likelihood Of Success Finding

Based upon its finding that "Glaxo has clearly shown infringement," the district court presumed irreparable harm. JA 43. Thus, the district court's erroneous likelihood of success determination infected its irreparable harm conclusion.

The presumption of irreparable harm arises only when the patentee makes a clear showing of both infringement and validity.[9] *See Datascope Corp. v. Kontron Inc.*, 786 F.2d 398, 400, 229 U.S.P.Q. 41, 42 (Fed. Cir. 1986). The district court erred in affording Glaxo the presumption of irreparable harm based on its erroneous likelihood of success finding. Glaxo is not entitled to the presumption because Ranbaxy's cefuroxime axetil antibiotic does not infringe any claim of the '181 patent. *See Novo Nordisk*,

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[9] Ranbaxy did not challenge the validity of the '181 patent in opposing the preliminary injunction motion because Ranbaxy was not given the opportunity to conduct any discovery regarding the validity of the '181 patent.

77 F.3d at 1371, 37 U.S.P.Q.2d at 1779 (the court erred in presuming irreparable harm based on its erroneous infringement finding); *High Tech. Med. Instrumentation, Inc. v. New Image Indus., Inc.*, 49 F.3d 1551, 1556, 33 U.S.P.Q.2d 2005, 2009 (Fed. Cir. 1995).

The district court also addressed actual irreparable harm, again in view of its finding that Ranbaxy infringes the '181 patent. JA 43. In so doing, the court provided no reasoning why money damages would be insufficient. *See Nutrition 21 v. Thorne Research, Inc.*, 930 F.2d 867, 872, 18 U.S.P.Q.2d 1347, 1351 (Fed. Cir. 1991) ("there is no *presumption* that money damages will be inadequate" and the moving party must proffer evidence and reasoned analysis for such inadequacy).

This Court has previously affirmed the sufficiency of money damages in similar circumstances. *See Eli Lilly and Co. v. American Cyanamid Co.*, 82 F.3d 1568, 1569-70, 38 U.S.P.Q.2d 1705, 1706 (Fed. Cir. 1996). In *Eli Lilly*, plaintiff's patent on the drug at issue and many of its process patents for producing the drug had expired. *See id.* at 1570, 38 U.S.P.Q.2d at 1706. Faced with other market entrants, Eli Lilly sought to enjoin the launch of competing products based on one of its remaining patents. *See id.* at 1570-71, 38 U.S.P.Q.2d at 1706-07. This Court affirmed the district court's

finding of no irreparable harm, noting that "[i]n light of the structure of the [drug] market, . . . that calculating lost profits would be a relatively simple task." *Id.* at 1578, 38 U.S.P.Q.2d at 1713; *see Nutrition 21*, 930 F.2d at 871, 18 U.S.P.Q.2d at 1351 ("neither the difficulty of calculating losses in market share, nor speculation that such losses might occur, amount to proof of special circumstances justifying the extraordinary relief of an injunction prior to trial."). The Court also accepted the district court's finding that the defendants' ability to respond in money damages negated irreparable harm. *See Eli Lilly*, 82 F.3d at 1578-79, 38 U.S.P.Q.2d at 1713-14.

The district court erroneously concluded that Ranbaxy Laboratories Limited may be unable to respond in money damages. JA 44-45. Ranbaxy Laboratories Limited is worth approximately $350 million, not including the estimated first year profit of $25 million from a cefuroxime axetil antibiotic launch. *Id.*; JA 678 (Chattaraj Decl., ¶ 8). [**CONFIDENTIAL MATERIAL OMITTED**] Thus, Ranbaxy could satisfy any monetary loss. The district court's analysis failed to account for the fact that Glaxo would encounter no loss unless and until Ranbaxy launches its product, and that any damages would not accrue over the life of the patent but, rather, only until a final judgment, which would likely have been less

than one year. Thus, Ranbaxy can answer in money damages, and the district court erred in finding irreparable harm.

2. The District Court's Conclusion On The Balance Of Hardships Was Premised On Its Erroneous Likelihood Of Success Finding

In assessing the balance of hardships, the district court recognized "that Ranbaxy faces certain hardships if a preliminary injunction is granted," but concluded that "the balance of hardships tips, perhaps just slightly, in [Glaxo's] favor. JA 47, 48. In reaching this conclusion, the court considered its likelihood of success finding. JA 47. Thus, the court's erroneous likelihood of success finding infected its balance of hardships determination and erroneously tipped the balance toward Glaxo. JA 47-48. Absent the court's erroneous finding on likelihood of success, the balance of hardships favors Ranbaxy.

3. The District Court's Conclusion On The Public Interest Was Premised On Its Erroneous Likelihood Of Success Finding

The district court premised its determination of the public interest factor entirely on its finding of likelihood of success. JA 49. As with the

other factors, the court's erroneous likelihood of success determination infected its determination of the public interest factor.

Moreover, the district court apparently misunderstood that the ANDA process favors the public interest and the denial of a preliminary injunction in this case. The ANDA process benefits the public because the process "make[s] available more low cost generic drugs," "increase[s] competition," "and best of all, the American people will save money, and yet receive the best medicine that pharmaceutical science can provide." *Glaxo*, 110 F.3d at 1568, 42 U.S.P.Q.2d at 1262. Patent holders benefit by obtaining "limited extensions of patent term in order to recover a portion of the market exclusivity lost during the lengthy process of development and FDA review." *Id.* Thus, the public obtains lower cost generic drugs through the ANDA process in exchange for limited patent term extensions.

Glaxo obtained the maximum two-year patent term extension for its '320 patent on cefuroxime axetil and [

CONFIDENTIAL MATERIAL OMITTED

] Thus, Glaxo has enjoyed the benefit of its bargain. When the '320 patent expired in May of 2000, the public was entitled to competition in the marketplace and a lower priced cefuroxime axetil antibiotic, the express

bargain established under the ANDA process. This is exactly what Ranbaxy seeks to provide. Preliminary injunctive relief denies the public the benefit of this bargain.

Glaxo now seeks to renege on its bargain with the public by attempting to extend its exclusivity over cefuroxime axetil by using the '181 patent. The problem with Glaxo's approach is that the narrow claims of the '181 patent do not cover the cefuroxime axetil antibiotic Ranbaxy seeks to market. Ranbaxy is entitled to compete with Glaxo in the marketplace, and to provide the public with the lower cost cefuroxime axetil antibiotic which was part of the bargain. *See Illinois Tool Works, Inc. v. Grip-Pak, Inc.*, 906 F.2d 679, 684, 15 U.S.P.Q.2d 1307, 1311 (Fed. Cir. 1990) (right to compete counterbalances interest in protecting patent rights when likelihood of success not shown). Glaxo has already received its benefit of the bargain, and the public is now entitled to receive its benefit.

"Neither the public interest nor equity favors grant of an injunction against one who does not infringe." *Novo Nordisk*, 77 F.3d at 1371, 37 U.S.P.Q.2d at 1779. Thus, the district court erred in assessing the public interest factor, which favors Ranbaxy.

V. CONCLUSION

The district court erred as a matter of law in construing the "essentially free from crystalline material" limitation of Claim 1 of the '181 patent to encompass cefuroxime axetil containing 10-15% crystalline material. This legal error pervaded the district court's analysis of the factors upon which the court based its grant of a preliminary injunction. Because the district court's determination was premised on a legal error, the court abused its discretion in granting a preliminary injunction. Therefore, this Court should vacate the preliminary injunction.

Because the district court indicated that its claim construction was final and was prepared to enter a permanent injunction based on its assessment of infringement under this claim construction, this Court should properly construe the disputed limitation of Claim 1. This Court should also

determine that no range of equivalence is available for the disputed limitation as a matter of law, and remand for further proceedings.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 1/8/01 By: Darrell L. Olson

Darrell L. Olson
William R. Zimmerman
Attorneys for Defendant-Appellant
RANBAXY PHARMACEUTICALS INC.

CERTIFICATE OF COMPLIANCE UNDER FED. R. APP. P. 32(a)(7)(C)

Defendant-Appellant Ranbaxy Pharmaceuticals Inc. submits its brief under Rules 32(a)(5)(A) and 32(a)(7)(B) of the Federal Rules of Appellate Procedure. As required by Rule 32(a)(7)(C), I hereby certify that Ranbaxy Pharmaceuticals Inc.'s brief complies with the type-volume limitation therein provided, and I further certify that Ranbaxy Pharmaceuticals Inc.'s brief contains approximately 12,773 words, including headings, footnotes and quotations.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 1/08/01

By: W.R. Zimmerman

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RANBAXY PHARMACEUTICALS INC.

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ADDENDUM

ADDENDUM

1. Preliminary Injunction Order, entered December 21, 2000. JA 1-2.

2. Memorandum And Order To Show Cause Order, entered December 18, 2000. JA 3-51.

3. U.S. Patent 4,562,181, issued December 31, 1985. JA 64-73.

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

GLAXO GROUP LIMITED and
GLAXO WELLCOME, INC.,

Plaintiffs,

v.

RANBAXY PHARMACEUTICALS, INC.,

Defendant.

The Honorable Mary L. Cooper
Civil Action No. 00-5172 (MLC)

PELIMINARY INJUNCTION ORDER

This matter having been opened to the Court by Saiber, Schlesinger, Satz & Goldstein, LLC and Hopgood, Calimafde, Judlowe & Mondolino, LLP, attorneys for plaintiffs, in the presence of Mathews, Collins, Shepherd & Gould, PA and Knobbe, Martens, Olson & Bear, LLP, attorneys for defendant for a Preliminary Injunction and the Court having read the submissions of the parties, heard argument of counsel and for the reasons stated in the Court's Memorandum and Order to Show Cause entered on the docket December 18, 2000;

IT IS on this ~~twentieth~~ 21st day of December, 2000;

ORDERED that defendant, its officers, agents, servants, employees, and attorneys and all persons including Ranbaxy Laboratories Limited, in active concert or participation with defendant, who receive actual notice of this Preliminary Injunction Order are restrained and enjoined during the pendency of this action from offering for sale or selling within the United States, its territories and possessions only any cefuroxime axetil product pursuant to Ranbaxy's ANDA No. 65-043; and it is

FURTHER ORDERED that this Preliminary Injunction Order be and is hereby conditioned upon plaintiffs posting with the Clerk of this Court within five (5) business days of the entry of this Order a surety bond in the amount of ten million dollars ($10,000,000.00) for payment of such costs and damages as may be incurred or suffered by any person or party who ~~may be~~ is found to be wrongfully restrained by this Order; and it is

FURTHER ORDERED that all proceedings in this case including the briefing schedule and Show Cause Order contained within the Court's Memorandum and Order to Show Cause of December 18, 2000 are stayed until further Order of the Court.

Dated: December 20, 2000
Trenton, NJ

Mary L. Cooper
Honorable Mary L. Cooper
U.S.D.J.

NOT FOR PUBLICATION

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

GLAXO GROUP LIMITED and GLAXO WELLCOME, INC,	:	CIVIL ACTION NO. 00-5172 (MLC)
Plaintiffs,	:	
v.	:	**MEMORANDUM AND ORDER TO SHOW CAUSE**
RANBAXY PHARMACEUTICALS, INC.,	:	
Defendant.	:	

COOPER, District Judge

This matter comes before the Court on the motion of plaintiffs Glaxo Group Limited and Glaxo Wellcome, Inc. (collectively "Glaxo") for a preliminary injunction enjoining defendant Ranbaxy Pharmaceuticals, Inc.'s ("Ranbaxy") from launching cefuroxime axetil under ANDA No. 65-043 because of the alleged infringement of Glaxo's U.S. Patent No. 4,562,181. The Court has considered the papers submitted by the parties and heard oral argument on December 12, 2000. The Court hereby issues its findings of fact and conclusions of law as required by Federal Rule of Civil Procedure 52. For the reasons given in this Memorandum and Order, the Court grants this preliminary injunction motion. The Court will file an appropriate order after determining the size of the bond as required by Federal Rule of Civil Procedure 65(c) or whether the order should be made final, thereby obviating the need for a bond. The Court issues

an Order to Show Cause directing the parties to address those two subjects.

BACKGROUND

Glaxo Wellcome, Inc. is the holder of a New Drug Application ("NDA") from the Food and Drug Administration ("FDA") for cefuroxime axetil, a product it sells under the brand name Ceftin®. (App. in Supp. of Pls.' Mot. for Prelim. Injunc. ("Pls.' App.") Ex B: Decl. of Barbara Rivera dated 11-21-00 ("Rivera Decl.") ¶ 2.) Glaxo Group Limited holds, as the assignee, United States Patent No. 4,562,181 ("'181 patent") (id.; Pls.' App. Ex. A: United States Patent No. 4,562,181 ("'181 Patent") [73]), entitled "Amorphous Form of Cefuroxime Ester" ('181 Patent [54]). This '181 patent expires on July 28, 2003. (Rivera Decl. ¶ 14.)

The '181 patent contains fourteen claims. The claims relevant to this motion are:

> 1. Cefuroxime axetil in amorphous form essentially free from crystalline material, and having a purity of at least 95% aside from residual solvents.
> 2. The product of claim 1 which contains less than 3% m/m of impurities.
> 3. The product of claim 1 in the form of a mixture of R and S isomers.
> 4. The product of claim 3 wherein the mole ratio of R to S isomers is from 3:2 to 2:3.
> 5. The product of claim 3 wherein the mole ratio of R to S isomers is from 0.9:1 to 1.1:1.
> . . . .
> 7. A method of combatting bacterial infections of the human or animal body which comprises administering to the said body orally or rectally an effective amount of

a highly pure substantially amorphous form of cefuroxime axetil as claimed in claim 1.

8. An antibacterial pharmaceutical composition containing an antibacterially effective amount of cefuroxime axetil according to claim 1 in admixture with one or more pharmaceutical carriers or excipients.

9. The antibacterial pharmaceutical composition of claim 8 wherein the cefuroxime axetil is present in the form of a mixture of R and S isomers.

10. The antibacterial pharmaceutical composition of claim 8 wherein the mole ratio of R to S isomers is from 3:2 to 2:3.

11. The antibacterial pharmaceutical composition of claim 8 wherein the mole ratio of R to S isomers is from 0.9:1 to 1.1:1.

. . . .

13. The antibacterial pharmaceutical composition of claim 8 adapted for oral administration.

14. The antibacterial pharmaceutical composition of claim 13 in dosage unit form containing from 40 to 500 mg of cefuroxime axetil.

('181 Patent cols. 13-14.)

Glaxo claims that Ranbaxy infringes this '181 patent by filing an Abbreviated New Drug Application ("ANDA") with the FDA for permission to market an antibiotic Glaxo asserts infringes the claims listed above. (Compl. ¶¶ 8-14; Pls.' Mem. in Supp. of Mot. for Prelim. Inj. ("Pls.' Mem.") at 14.) Because the other claims are dependent on claim 1, the parties' arguments focus almost entirely on claim 1 (Pls' Mem. at 14; Def.'s Mem. in Opp'n to Mot. for Prelim. Inj. ("Def.'s Mem.") at 6-21.), and the Court's analysis of claim 1 ultimately disposes of the motion, the following discussion will focus on claim 1. The Court will now provide introductory information about the nature of the drug at issue, the claims and specifications of patent '181, the

prosecution history of patent '181, the nature of Ranbaxy's FDA filing and proposed product, and the characteristics of the parties relevant to a preliminary injunction inquiry.

I. Cefuroxime Axetil

Cefuroxime axetil is an antibiotic used to combat a variety of microorganisms causing such conditions as pharyngitis, tonsilitis, acute bacterial maxillary sinusitis, and uncomplicated skin and skin-structure infections. (Pls.' App. Ex. J: Excerpts from Volume 1 of Ranbaxy's ANDA No. 65-043 ("ANDA Vol. 1") at R03770-R03771.) The compound cefuroxime, while an effective medication when injected, could not be given in oral form because the compound alone is not easily absorbed by the gastro-intestinal tract and thereby does not enter the body's blood stream in sufficient numbers. ('181 Patent col. 1 lines 8-25.) It was found, however, that combining the cefuroxime with an ester increases the amount of absorption of the antibiotic compound through the gastro-intestinal lining and into the circulatory system. (Id. lines 26-45.)

One of these combinations of cefuroxime with an ester is cefuroxime axetil. (Id. lines 62-68.) Glaxo Laboratories Limited was the assignee of United States Patent No. 4,267,320 ("'320 patent"), claiming the compound cefuroxime axetil. (Decl. of William R. Zimmerman dated 11-20-00 ("Zimmerman Decl.") Ex. 4: United States Patent No. 4,267,320 ("'320 Patent"), Def.'s Mem.

at 3.) The '320 patent expired in May of 2000. (See, e.g., Def.'s Mem. at 4.)

The '181 patent, however, is the patent at issue in this case. The most important aspect of this patent for our purposes is the claimed mixture of amorphous cefuroxime axetil and crystalline cefuroxime axetil.[1] This makeup is relevant because it helps to determine the bioavailability of the cefuroxime itself. Bioavailability refers to the rate and extent to which the active ingredient is absorbed from the drug product and is "available at the site of action." (Pls.' Prelim. Inj. Graphics Display ("Pls.' Graphics Display") Tab 3 (quoting 21 C.F.R. 320.1).) Applied to this drug in layperson's terms, the concept deals with the necessity of ensuring that oral, ingested medicine survives the very hostile environment of the stomach and gastrointestinal tract, dissolves quickly enough in the appropriate place in the small intestines, and can be absorbed into the bloodstream through the intestinal wall. (Pls.' Mem. at 4 n.6; Pls.' Graphics Display Tab 5.)

The inventors of the subject matter of the '181 patent concluded that, contrary to previous experience, amorphous

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[1] Solid substances can exist in either an amorphous form or a crystalline form. (Declaration of Robert William Lancaster dated 12-11-00 ¶ 4.) A crystal is defined as "a solid made up of an orderly repeating arrangement of molecules." (Id.) An amorphous solid, on the other hand, "has no long range order associated with it." (Id.)

cefuroxime possesses a better bioavailability than its crystalline counterpart. ('181 Patent col. 2 lines 9-15.) In other words, more cefuroxime axetil reaches the bloodstream and therefore actually helps the patient when in amorphous as opposed to crystalline form. Therefore, the issued claim 1 of the '181 patent covers "[c]efuroxime axetil in amorphous form essentially free from crystalline material . . . ." (Id. col. 13, lines 4-6.)

II. The Specification of the '181 Patent

The written description in the '181 patent, also known as the specification, contains a number of non-quantitative references to the level of crystalline material covered by the pattern. The applicants, however, apparently did not amend this specification during the patent's prosecution. The specification states, "[a]ccording to one aspect of the present invention, there is provided cefuroxime axetil in highly pure, substantially amorphous form." ('181 Patent col. 2, lines 23-25.) Two paragraphs below this statement, the specification further provides that "[t]he cefuroxime axetil ester in accordance with the invention is preferably essentially free from crystalline material." (Id. lines 39-42.) The specification also contains a number of references to cefuroxime axetil as "substantially amorphous." (See, e.g., id. col. 2, lines 62-63; col. 3 lines 7-8, 9-10.)

The specification also contains examples of various ways to prepare cefuroxime axetil, some of which may be relevant to the language in claim 1. Example 1 states:

> X-ray powder analysis in a 0.3 mm diameter capillary by the Debye Scherrer method in a 114.6 mm diameter camera by exposure for 3 hrs. . . . radiation gave a plain halo (absence of crystals, confirming the amorphous nature of the product).

(Id. col. 8, lines 5-9.) Example 18 states that:

> The infrared spectrum (Nujol) confirmed the amorphous nature of the product [cefuroxime axetil]. X-ray powder analysis showed a few faint lines which may suggest the presence of a few crystals.

(Id. col. 9, lines 27-31.) Example 21 states that "[m]icroscopic examination suggested <1% crystalline material." (Id. col. 10, lines 4-6.) Example 22 states that "X-ray crystallography revealed the product was substantially amorphous with a small content of crystalline material." (Id. lines 26-29.) Example 26 likewise provides that "[t]he infra-red (Nujol) spectrum confirmed the substantially amorphous nature of the product." (Id. col. 11, lines 39-40.) Example 19 refers to "pure amorphous material" and microscopic examination (id. col. 9, lines 39-45) while other examples mention the material's amorphous nature confirmed by various tests (Id. cols. 9-11 (Examples 20, 23-25)).

IV. The Prosecution History of Patent '181

This patent claim commenced with an application received by the United States Patent and Trademark Office ("PTO") on July 29,

1983. (Zimmerman Decl. Ex. B: Prosecution History of United States Patent No. 4,562,181 ("Prosecution History") at 5.) The initial application contained nine claims. The most relevant claims are:

> 1. Cefuroxime axetil in highly pure, substantially amorphous form.
>
> . . . .
>
> 4. The product of claim 1 essentially free from crystalline material.
>
> . . . .
>
> 9. A method of combatting bacterial infections of the human or animal body which comprises administering to the said body orally or rectally an effective amount of a highly pure substantially amorphous form of cefuroxime axetil.

(Id. at 32.)

In an office action dated May 10, 1984, the PTO examiner rejected all nine claims in the initial application. (Id. at 89.) The Examiner rejected the "highly pure, substantially amorphous form" language on the grounds of indefiniteness under 35 U.S.C. § 112. He stated:

> It is not definite what is particularly included or excluded by the term "highly pure, substantially amorphous form". [sic] It is noted that there is no particular limit indicated for the amounts of impurities while applicants do not regard residual solvents as impurities (page 3, lines 24-36). It is also not clear how much crystalline material is permitted. Dependent claim 4 specifies a product which is essentially free from crystalline material. The cefuroxime axetil as employed in the method of claim 9 is further mixed with other materials.

(Id. at 90.) The examiner also rejected the nine claims on the grounds of obviousness in light of prior art, stating:

> No particular criticality is evident due to the claimed highly pure substantially amorphous form of cefuroxime axetil to make said material unobvius [sic] from the reference material which is indicated in the instant specification as being either in relatively impure amorphous form or in the form of purer crystalline material (page 2, lines 28-34). It is noted that no data has been presented to indicate any criticality due to purity while it is not even evident what is particularly included by the term "a amorphous form["] [sic].

(Id. at 91.) After this rejection, an examiner's interview was conducted and the applicants agreed to submit a claim indicating an amorphous form containing less than 5% m/m, of impurities except for residual solvents and less than 6% residual solvents. (Id. at 93.)

The applicants submitted a response, received November 15, 1984, containing both claim amendments and a traverse to the examiner's obviousness rejection. (Id. at 105-13.) They canceled claims 1, 2, and 4 and added claim 10. (Id. at 105.) The new claim 10 claims:

> Cefuxomine axetil in amorphous form essentially free from crystalline material, which contains less than 5% m/m of impurities other than residual solvents and less than 6% m/m of residual solvents.

(Id.) The applicants amended claims 3, 5, and 8 so that they depended on claim 10. (Id. at 106.) They also added "as claimed in Claim 10" to the end of claim 9. (Id.) New claims 11 through 17 were added as well, which were issued as claims 8 through 14. (Id. at 106-07.) The applicants argued that the indefiniteness

rejection should be withdrawn due to these amendments. (Id. at 108.) But applicants traversed the obviousness rejection, presenting the declaration of Dr. Gordon Ian Gregory. (Id. at 108-21.)

The PTO examiner again rejected the claims with an office action dated January 24, 1985. (Id. at 122-25.) Claims 3 and 5 through 15 were rejected under 35 U.S.C. § 112 because they failed to describe the invention in "such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." (Id. at 123.) The examiner continued by stating:

> The claims are drawn to all forms of cefuroxime axetile(CA) that are amorphous & within certain impurity limitations. The specification of page 8, lines 15-20, states that the CA used to produce amorphous CA by applicant's technique must be of the same high purity as the amorphous product. The only example given produces the high purity CA by crystallization. It is not apparent that other purification techniques applied to Gregson's Exl CA (which to [sic] is now said to be 70% pure) will yield, after applicant's technique, the superior CA claimed. that [sic] is, no assurance is seen that repeated washings, dialysis etc, of Gregson's Exl CA, even if purity within the scope of the claims is reached, would yield the superior CA. There is no teaching how the level of purity is reached other than by crystallization (paragraphs 1 & 2).

(Id. at 123.) As in the first rejection, the examiner also based his decision on the grounds of obviousness. (Id. at 123-24.)

After this second rejection, a personal interview with the examiner was conducted on April 19, 1985, and the parties agreed to amend the first claim,[2] discussed a declaration that would be submitted stating that desired results can be achieved by other means, and talked about a prior art patent. (Id. at 127.) After this interview, the applicants submitted a second and final response to the PTO, received in the mailroom on July 5, 1985. (Id. at 129.) The only amendment was to change claim 10 to its present form:

> Cefuroxime axetil in amorphous form essentially free from crystalline material, and having a purity of at least 95% aside from residual solvents.

(Id. at 129.) In their remarks, applicants stated that this wording was agreed to at the interview. (Id. at 129-30.) As before, the applicants traversed the obviousness rejection of claims 3 and 5 through 17, presenting a declaration from Edward McKenzie Wilson. (Id. at 130-41.) The PTO then allowed the claims to be issued, apparently without any further amendment or rejection. (Id. at 143-44.) The claims issued are quoted above, with claim 10 being issued as claim 1.

While making its first rejection of the patent application, the PTO examiner advised the applicants "of possible benefits under 35 U.S.C. [§] 119, wherein an application for [a] patent

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[2] This is presumably a reference to claim 10, which would eventually be issued as claim 1.

filed in the United States may be entitled to the benefit of the filing date of a prior application filed in a foreign country." (Id. at 90.) Responding to this suggestion, applicants submitted a certified copy of United Kingdom Patent Application No. 8222019 ("United Kingdom patent"), with a cover letter dated November 15, 1984. This foreign patent application, filed with the Patent Office of the United Kingdom on July 30, 1982, states:

> The cefuroxime 1-acetoyethyl ester in accordance with the invention is preferably essentially free from crystalline material, by which we mean that any amount of crystalline material which may be present is so low as to be undetectable by X-ray crystallography, i.e. that an X-ray photograph of a sample of the compound shows no rings. The crystalline content of such a sample [of cefuroxime axetil] may be assumed to be zero for all practical purposes.

(Prosecution History at 101.)

V. RANBAXY'S PRODUCT

Ranbaxy, through its parent Ranbaxy Laboratories Limited, filed an ANDA, containing the file number 65-043, with the FDA seeking approval to market an antibiotic drug containing cefuroxime axetil on April 19, 1999. (See, e.g., ANDA Vol. 1 at R03736; Decl. of Shirley Ternyik dated 11-29-00 ("Ternyik Decl.") ¶ 2.) The ANDA process permits a pharmaceutical company to receive approval to market a drug product without conducting clinical trials by merely showing that the drug product is bioequivalent to an already approved drug in the sense of delivering a comparable amount of active moiety to a patient as

the already approved medication. (Ternyik Decl. ¶ 4.) According to the ANDA, Ranbaxy wishes to use cefuroxime axetil as an active ingredient in doses of 125 mg, 250 mg, and 500 mg. (ANDA Vol. 1 at R03771.) These medications are in tablet form for oral administration and are intended to combat bacterial infections. (ANDA Vol. 1 at R03768-R03771.) According to the Drug Master File, the proposed medication contains between 0.32% and 2.0% related impurities, excluding residual solvents. (Pls.' App. Ex. M: Excerpts from Volume 2 of Ranbaxy's Crystalline Cefuroxime Axetil Drug Master File ("Drug Master File") at R04849.)

Ranbaxy's proposed product also contains a mixture of 12% crystalline cefuroxime axetil and 88% amorphous cefuroxime axetil. (Pls.' App. Ex K: Ranbaxy's Nov. 6, 2000 Fax Amendment to ANDA No. 65-043 ("Ranbaxy's Fax Amendment") at R5965, R5969; Zimmerman Decl. Ex. 6: Certain Portions of ANDA, No. 65-043 ("ANDA Application") at R03915-R03917, R04074-R04099; Ternyik Decl. ¶ 5.) The ANDA permits the content of crystalline cefuroxime axetil to be no more than 15% and no less than 10%. (Ternyik Decl. ¶ 5; Ranbaxy's Fax Amendment at R5962, R5988-R5993.) This crystalline material is an active ingredient of the product, delivering a portion of cefuroxime to the patient. (Ternyik Decl. ¶ 6.) Ranbaxy stated in a Fax Amendment submitted to the FDA that:

> Ranbaxy's dissolution and stability testing establishes that the percentage of crystalline and amorphous forms

> in its tablets (12% and 88%, respectively) does not adversely affect the identity, strength, quality, purity, potency and performance of the drug product . . . . In particular, the percentage of crystalline component in Ranbaxy's tablets shows no adverse impact on the solubility or in-vivo characteristics of the drug product, since the drug product complies with the bioequivalence criteria.

(Ranbaxy's Fax Amendment at R5969.)

The FDA has not approved Ranbaxy's ANDA, and the company cannot launch its cefuroxime axetil product until it receives this approval. (Decl. of Dipak Chattaraj dated 11-29-00 ("Chattaraj Decl.") at ¶¶ 4-5; Ternyik Decl. ¶ 3.) The President of Ranbaxy, Dipak Chattaraj ("Cattaraj"), claimed that the timing of the approval can not be determined (Chattaraj Decl. ¶ 4), that Ranbaxy would need at most forty-five days to manufacture the necessary quantity of products for a launch, that the company has ceased manufacturing, and has not contacted distributors, established a price list, or prepared any marketing material (Dep. of Dipak Chattaraj dated 11-9-00 ("Chattaraj Dep.") at 46-61.) Chattaraj, however, also stated that he has told customers that FDA approval could come "any day now." (Id. at 61.) In addition, an article in the Economic Times on October 13, 2000 states that Ranbaxy Laboratories was expecting approval for marketing in November of 2000. (Pls.' App. Ex. E: James Matthews, Bayer to Pump $5 million in Ranbaxy, Economic Times, Oct. 13, 2000, available at,

http://www.economictimes.com/today/13comp06.htm.) Reuters, however, reported on October 27, 2000 that Ranbaxy Laboratories does not expect FDA approval this year because of the citizen's petition filed by Glaxo Wellcome, Inc. in opposition to any approval. (Id. INDIA: Ranbaxy Sees No FDA Approval This Year for Cef Axetil, 10/27/00 RTENGNS 10:48:00.)

IV. The Companies

Glaxo Wellcome, Inc. is a pharmaceutical company with 1999 sales of $5.8 billion. (Zimmerman Decl. Ex. 25: Corporate Information, at http://glaxowellcome.com/corpinfo.htm (visited Nov. 29, 2000) at 2.) Its parent company, Glaxo Wellcome plc had total sales in 1999 of $13.75 billion. (Id.) Barbara Rivera ("Rivera"), a senior product manager at Glaxo Wellcome, Inc., declared that Glaxo's Ceftin® tablet sales exceed[ ] annually in the United States, that it sold[ ]of Ceftin® last year worldwide, and that its total Ceftin® sales in the United States since 1988 have been in excess of[ ] (Rivera Decl. ¶¶ 1, 4.) She stated that, based on prior experience, the entry into the [United States] market of Ranbaxy's proposed product will cause Glaxo to lose[ ] in sales and[ ]of its market share in the first three months, [ ]between the third and sixth months and[ ]of its market share by the end of these six months, and[ ]and [ ]of its market share between the sixth and twelfth months.

(Rivera Decl. ¶ 13.) Glaxo therefore may lose [ ] in sales during the first year of the alleged infringement. (Id.) It also may lose approximately [ ] in sales during the remaining life of the '181 patent, which expires on July 28, 2003, due to Ranbaxy's market entry. (Id. ¶ 14.)

Ranbaxy contests these figures. (Chattaraj Decl. ¶ 7.) It contends that they are speculative and that Glaxo is likely to lose less because the buying season for cefuroxime axetil has passed. (Id.) It also appears that Glaxo has given Professional Detailing, Inc. ("Professional Detailing"), the marketing, sales, and distribution rights to Ceftin® in the United States, although Glaxo has kept its intellectual property rights and continues to be the manufacturer of the product. (Zimmerman Decl. Ex. 26: Professional Detailing: Significant Developments, at http://yahoo.marketguide.com/mgi/s..asp?nss+yahoo&rt+signdevt&rn+A!A9A (visited Nov. 28, 2000); Ex. 27: Herb Greenberg, Why Professional Detailing's Future Sales Might Not Be What They Appear, at http:/www.RealMoney.com (originally posted Oct. 3, 2000).)

The defendant Ranbaxy Pharmaceuticals, Inc. is the United States-based, wholly owned subsidiary of India-based Ranbaxy Laboratories Limited. (Chattaraj Decl. ¶ 2.) Ranbaxy develops and markets both innovative and generic pharmaceuticals. (Id.) Chattaraj believes that his company will obtain 25% of the

[United States] cefuroxime axetil market in the first year of marketing. (Chattaraj Decl. ¶ 7; Chattaraj Dep. at 58.) He expects its profit from the first year of [United States] sales of Cefuroxime Axetil to be $25 million. (Chattaraj Decl. ¶ 8.) According to Chattaraj, Ranbaxy would gain significant advantages from being the first generic maker of cefuroxime axetil. (Id. ¶¶ 9-12). As the first generic supplier, Ranbaxy would supposedly be able to charge a premium price until a second generic competitor enters the market, foster relationships with retailers thereby increasing sales of both the particular drug in question and new drugs to be introduced into the future, and maintain a very high share of the generic market even after the entry of other generic suppliers because most retailers stock only one generic version of a medication. (Id.) According to Glaxo, Ranbaxy had total sales of $23.2 million in calendar year 1999, with a net loss of $900,000. (Pls.' App. Ex. C: Excerpts from Ranbaxy Laboratories Limited 1999 Annual Report at 33.) Ranbaxy Laboratories Limited has total sales of $334 million annually, with a profit of $56 million. (Id. at 35, 44.) Glaxo concludes that Ranbaxy's combined liquid net worth is less than $175 million. (Id.)[3] Chattaraj, however, asserted that the net worth

[3] These figures for Ranbaxy Laboratories Limited are reported in Indian rupees, and Glaxo converted the figures to American currency based on an exchange rate of 46.7 rupees to a United States dollar. (Pls.' Mem. at 3 n.3.)

of Ranbaxy Laboratories Limited, which will answer for any damages against Ranbaxy (Def.'s Mem. at 22 n.12), is $350 million as of September 30, 2000. (Chattaraj Decl. ¶ 8.)

DISCUSSION

Glaxo's Complaint appears to seek injunctive relief for patent infringement pursuant to 35 U.S.C. § 283. (Compl.) This provision authorizes courts "to grant injunctions in accordance with the principles of equity to prevent the violation of any right secured by patent, on such terms as the court deems reasonable." 35 U.S.C. § 283. The alleged violation in this case is patent infringement under 35 U.S.C. § 271(a), which states that "whoever without authorization makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent therefor, infringes the patent."

Perhaps more relevant to this motion, Glaxo's Complaint also alleges patent infringement under the specialized and complex provisions of the Drug Price Competition and Patent Term Restoration Act. (Compl. ¶ 14.) 35 U.S.C. § 271(e)(2) states in relevant part:

> It shall be an act of infringement to submit -
>
> > (A) an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act or described in section 505(b)(2) of such for a drug claimed in a patent or the use of which is claimed in a patent; . . .
> >
> > . . . .

> if the purpose of such submission is to obtain approval under such Act to engage in the commercial manufacture, use, or sale of a drug . . . claimed in a patent or the use of which is claimed in a patent before the expiration of such patent.

Id. 35 U.S.C. § 271(e)(4) provides a list of three exclusive remedies for the act of infringement prohibited in 35 U.S.C. § 271(e)(2).[4] 35 U.S.C. § 271(e)(4)(B) does state that "injunctive relief may be granted against an infringer to prevent the commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug . . . ." Ranbaxy does not expressly challenge Glaxo's claim for preliminary injunctive relief under this statutory provision, and the Court finds that Glaxo may pursue its injunctive motion subject to the general principles of equitable relief applicable in patent cases.[5]

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[4] 35 U.S.C. § 271(e)(4) states that "[t]he remedies prescribed by subparagraphs (A), (B), and (C) are the only remedies which may be granted by a court for an act of infringement described in paragraph (2), except that a court may award attorney fees under section 285." 35 U.S.C. § 271(e)(4)(A) provides that "the court shall order the effective date of any approval of the drug . . . involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed." 35 U.S.C. § 271(e)(4)(C) authorizes the court to award damages or other monetary relief "against an infringer only if there has been commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug . . . ."

[5] The Court notes that the statutory scheme created by 35 U.S.C. § 271, described by one court as "complex," Upjohn Co. v. Mova Pharm. Corp., 899 F. Supp. 46, 48 (D.P.R. 1995), raises a range of questions not mentioned by either party. Two particular

Preliminary injunctive relief is available in cases of patent infringement. In order to obtain a preliminary injunction, a party must establish the right to such a relief based on four factors:

> (1) reasonable likelihood of success on the merits; (2) irreparable harm; (3) the balance of hardships tipping in its favor; and (4) the impact of the injunction on the public interest.

Hybritech, Inc. v. Abbott Labs., 849 F.2d 1446, 1451 (Fed. Cir. 1988) (footnotes omitted); see also Polymer Techs., Inc. v. Bridwell, 103 F.3d 970, 973 (Fed. Cir. 1996). Each factor taken individually is not dispositive, and the court must weigh each factor against each other and against the magnitude and form of the requested relief. Hybritech, Inc., 849 F.2d at 1451. The Federal Circuit has held that "[t]he standards applied to the

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complexities are the fact that, while the statute prohibits a submission with the purpose of engaging in the manufacture, use, or sale of a drug claimed by a patent before its expiration, it clearly states that no infringement occurs when the party is making, selling, or engaging in other activities "solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use or sale of drugs or veterinary biological products." 35 U.S.C. § 271(e)(1). Likewise, the provision authorizing injunctive relief preventing the manufacture or similar uses of "an approved drug" raises the question of whether this relief is available for a drug not yet approved by the FDA, such as Ranbaxy's own product. But, given the absence of any argument on these points, the Court will not conclude that the statute is a bar to potential injunctive relief. See also Upjohn Co., 899 F. Supp. at 49 (stating that injunctive relief under 35 U.S.C. § 271(e)(1) is available when ANDA applicant infringes patent by filing false certification as to patent's applicability and validity and there is, or might be, actual commercial manufacture, use, or sale).

grant of a preliminary injunction are no more nor less stringent in patent cases than in other areas of the law." H.H. Robertson Co. v. United Steel Deck, Inc., 820 F.2d 384, 387 (Fed. Cir. 1987), abrogated on other grounds by Markman v. Westview Instruments, Inc., 52 F.3d 967 (1995) (en banc), aff'd, 517 U.S. 370 (1996). While a preliminary injunction is considered an extraordinary remedy, see, e.g., Intel Corp. v. ULSI Sys. Tech., Inc., 995 F.2d 1566 (Fed. Cir. 1993), this characterization does not mean that the form of relief is unattainable, Polymer Techs., Inc., 103 F.3d at 977. The question of whether to grant preliminary injunctive relief is vested within the sound discretion of the district court. See, e.g., Oakley, Inc. v. Int'l Tropic-Cal, Inc., 923 F.2d 167, (Fed. Cir. 1991).

I. Reasonable Likelihood of Success on the Merits

Glaxo contends that a reasonable likelihood of success on the merits exists because Ranbaxy's proposed manufacture, use, and sale of its product literally infringes Glaxo's '181 patent. This Court agrees and finds that the reasonable likelihood of success requirement has been satisfied.[6]

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[6] Technically, a showing of infringement alone is often insufficient for satisfying the first preliminary injunction factor. The patentee should also show that the relevant patent is valid and enforceable. See, e.g., Nutrition 21 v. United States, 930 F.2d 867, 869-70 (Fed. Cir. 1991). In this case, Ranbaxy asserts a defense of invalidity (Answer ¶ 15; Pl.'s App. Ex. O: Ranbaxy's Written Response to Topic No. 3 of Glaxo's Notice of Rule 30(b)(6) Deposition), but these assertions are in other contexts. It notes in its brief that a study submitted by

It is now well-settled that patent claim construction is a legal question to be determined exclusively by the court. Markman v. Westview Instruments, Inc., 52 F.3d 967 (Fed. Cir. 1995) (en banc), aff'd, 517 U.S. 370 (1996). The determination of infringement requires a two-step analysis. Id. at 976. First, the claims must be construed, i.e., the legal meaning and scope of each cited claim must be determined. Id. Second, it must be determined whether the claims so construed cover an accused product or process, i.e., whether, in fact, every limitation found in a claim is present in the accused product or process. Id.

To determine the proper meaning of a claim term, a court must "consider the so-called intrinsic evidence, i.e., the claims, the written description, and, if in evidence, the prosecution history." Digital Biometrics, Inc. v. Identix, Inc., 149 F.3d 1335, 1344 (Fed. Cir. 1998). A court commits error if it uses extrinsic evidence, such as expert testimony, unless the

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Glaxo in support of its petition to the FDA opposing Ranbaxy's ANDA suggests that amorphous cefuroxime axetil was invented by others before the filing of the '181 patent. (Def.'s Mem. at 21 n.10 (citing Zimmerman Decl. Ex. 9: Citizen Petition at 38-50.) Specifically, this study, dated October 20, 1980 and apparently performed by scientists at Glaxo Group Research Ltd. involved the human testing of the urinary recovery of cefuroxime. (Id. at 41.) But Ranbaxy purposely refrains from challenging the validity of the '181 patent in its opposition because of the absence of discovery. (Id.) Given this decision, the Court will not question the validity of the patent, at least in the context of this motion.

intrinsic evidence is insufficient. Bell & Howell Document Mgmt. Prods. Co. v. Altek Sys., 132 F.3d 701, 705 (Fed. Cir. 1997); Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1583-84 (Fed. Cir. 1996). In defining claims, courts should first look to the words of the claims. Vitronics Corp., 90 F.3d at 1582. The "general rule is . . . that terms in the claim are to be given their ordinary and accustomed meaning," Johnson Worldwide Assocs., Inc. v. Zebco Corp., 175 F.3d 985, 989 (Fed. Cir. 1999) (citations omitted), unless it is clear from the written description or specification or the prosecution history that the patentee defined the claim term differently or if the ordinary meaning would deprive the term of clarity, K-2 Corp. v. Salomon S.A, 191 F.3d 1356, 1362-63 (Fed. Cir. 1999); Johnson Worldwide Assocs., Inc., 175 F.3d at 989-90. A court should consider the claim language according to its ordinary meaning as understood by those of ordinary skill in the art. See, e.g., Zelinski v. Brunswick Corp., 185 F.3d 1311, 1315 (Fed. Cir. 1999).

In determining the ordinary meaning of words as understood by one skilled in the art, dictionaries are an appropriate source of information. Although technically forms of extrinsic evidence, dictionaries fall in a special category. Vitronics Corp., 90 F.3d at 1584 n.6. Admittedly, "a patentee may choose to be his own lexicographer and use terms in a manner other than their ordinary meaning, as long as the special definition of the

term is clearly stated in the patent specification or file history." Id. at 1582. But, in the absence of this clear intent, "the term takes on its ordinary meaning" as found in its dictionary definition. Optical Disc Corp. v. Del Mar Avionics, 208 F.3d 1324, 1334 (Fed. Cir. 2000); see also, e.g, Karlin Tech. Inc. v. Surgical Dynamics, Inc., 177 F.3d 968, 971 (Fed. Cir. 1999) (using dictionaries to define claim terms).

After examination of the words, the court turns to the specification and, if in evidence, the prosecution history. See, e.g., Vitronics Corp., 90 F.3d at 1582-1583. Matters disclaimed during prosecution are excluded as a possible interpretation. See, e.g., Southwall Techs., Inc. v. Cardinal IG Co., 54 F.3d 1570, 1576 (Fed. Cir. 1995). Although similar, use of prosecution history for purposes of interpretation differs from the doctrine of prosecution history estoppel applicable under the doctrine of equivalents. See, e.g., Biodex Corp. v. Loredan Biomedical, Inc., 946 F.2d 850, 862 (Fed. Cir. 1991).

Applying these principles, the Court must turn to the most difficult question raised by this motion: the meaning of the phrase "[c]efuroxime axetil in amorphous form essentially free from crystalline material" in claim 1 of the '181 patent. Glaxo argues, and the Court finds, that this phrase must be given its ordinary meaning as merely excluding from the claimed invention any item having sufficient crystalline cefuroxime axetil that

materially or fundamentally affects the basic characteristics of the invention. If the cefuroxime axetil contains crystalline material that does not fundamentally affect the basic characteristics of the invention, the language does not exclude the cefuroxime axetil from the claim's coverage and a possible finding of infringement.

The Court reaches this conclusion because it finds that "essentially" is defined as "fundamentally," Webster's Third New International Dictionary 777 (1986), and "essential" is defined as "belonging to or being a part of the essence of something," id. Therefore, an interpretation of the claim language as focusing on whether the crystalline material fundamentally affects the characteristics and functions of the cefuroxime axetil invention conforms with the ordinary meaning of the words as revealed by the dictionary. This interpretation is also consistent with the judicial interpretation of the term of art "consisting essentially of" as excluding elements that would materially affect the characteristics of the invention in question. Water Techs. Corp. v. Calco Ltd., 850 F.2d 660, 666 (Fed Cir. 1988); PPG Indus., Inc. v. Guardian Indus. Corp., 156 F.3d 1351, 1354 (Fed Cir. 1998).

Ranbaxy advances a number of arguments against this interpretation of the phrase, most dependent on the prosecution history and file wrapper of the '181 patent. This Court, after

consideration of these arguments, finds that they fail to demonstrate that the patentee sought to define the phrase in question in a manner different than its ordinary meaning. See, e.g., K-2 Corp, 91 F.3d at 1362-63.

Ranbaxy's strongest argument is based on the apparently express definition of "essentially free from crystalline material" in the United Kingdom patent. In this foreign patent, the phrase is apparently defined to mean that "any amount of crystalline material which may be present is so low as to be undetectable by X-ray crystallography, i.e. that an X-ray photograph of a sample of the compound shows no rings" and that "t]he crystalline content of such a sample [of cefuroxime axetil] may be assumed to be zero for all practical purposes." (Prosecution History at 101.) Ranbaxy contends that this United Kingdom patent definition clearly establishes that Glaxo's claim may only be infringed by cefuroxime axetil containing undetectable amounts of crystalline material. (Def.'s Mem. at 8-10.)

This definition does not overcome the ordinary and reasonable interpretation of the phrase as not excluding from the claim crystalline cefuroxime axetil not affecting the fundamental functions and characteristics of the medication. Admittedly, a foreign patent application submitted for priority reasons under

35 U.S.C. § 119[7] arguably becomes part of the prosecution history

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[7] The current 35 U.S.C. § 119 provides in relevant part:

> (a) An application for patent for an invention filed in this country by any person who has, or whose legal representatives or assigns have, previously regularly filed an application for a patent for the same invention in a foreign country which affords similar privileges in the case of applications filed in the United States or to citizens of the United States, shall have the same effect as the same application would have if filed in this country on the date on which the application for patent for the same invention was first filed in such foreign country, if the application in this country is filed within twelve months from the earliest date on which such foreign application was filed; but no patent shall be granted on any application for patent for an invention which had been patented or described in a printed publication in any country more than one year before the date of the actual filing of the application in this country, or which had been in public use or on sale in this country more than one year prior to such filing.
>
> (b) No application for patent shall be entitled to this right of priority unless a claim therefor and a certified copy of the original foreign application, specification and drawings upon which it is based are filed in the Patent and Trademark Office before the patent is granted, or at such time during the pendency of the application as required by the Commissioner not earlier than six months after the filing of the application in this country. Such certification shall be made by the patent office of the foreign country in which filed and show the date of the application and of filing of the specification and other papers. The Commissioner may require a translation of the papers filed if not in the English language

of the United States patent, 35 U.S.C. § 119(b), and therefore a part of the intrinsic evidence available for claim construction, see Evans Med. Ltd. v. American Cyanamid Co., 11 F. Supp. 2d 338, 345-46 (S.D.N.Y. 1998) (discussing United Kingdom patent application), aff'd, 215 F.3d 1347 (Fed. Cir. 1999) (unpublished table decision); see also Augustine Med., Inc. v. Gaymar Indus., Inc., 181 F.3d 1291, 1300 (Fed. Cir. 1999) (stating that prosecution history of parent application may limit scope of later application using same clam term); Tanabe Seiyaku Co. v. United States Int'l Trade Comm'n, 109 F.3d 726, 733 (Fed. Cir. 1997) (stating that representations to foreign patent offices should be considered under equivalents doctrine); Jonsson v. Stanley Works, 903 F.2d 812, 818 (Fed. Cir. 1990) (considering prosecution history of another patent); Caterpillar Tractor Co. v. Berco, 714 F.2d 1110, 1116 (Fed. Cir. 1983) (considering foreign patent representations in context of doctrine of equivalents.) This definition is not contained in the '181 patent application or other parts of the patent history, but only in a 1982 foreign application about which we know very little.[8]

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and such other information as he deems necessary.

[8] According to the letter submitted as part of the request to the United Kingdom's Patent Office for a certified copy of the application, this foreign patent application was filed solely in order to establish a priority date and was thereafter abandoned. (Def.'s App. Ex. 3: Letter from Dr. C. L. Brewer to the Comptroller of the Patent Office misdated 5-18-94 and receive

In fact, the United Kingdom patent does not apparently even have Example 22, referring to "substantially amorphous" material. ('181 Patent col. 10, lines 27-28.)

The standard expressed in the United Kingdom patent definition also fails to disturb our conclusion because of materials submitted by Glaxo. Robert William Lancaster ("Dr. Lancaster"), a Research Leader in the Pharmaceutical Sciences Department at the Glaxo Wellcome Medicines Research Centre, stated that a 1983 Glaxo experiment using Debye-Scherrer X-ray photography to test various mixtures of crystalline and amorphous cefuroxime axetil shows that, from the photographs, it is difficult to distinguish between the samples containing 5%, 10%, and 15% crystalline material. (Decl. of Robert William Lancaster dated 12-11-00 ("Lancaster Decl.") ¶¶ 1, 7.) The Court's own examination of these photographs confirms this observation, although the lines do appear more distinct in the pictures of samples containing a greater proportion of crystalline material. (Lancaster Decl. Ex. C.) Dr. Lancaster believes that, with good preparation of the sample and film proceesing, the detection level for this photography is about 10% to 15% crystalline material, but that, without this preparation and processing, it

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19-84 ¶ 2.) Apparently the only reason the document could still be obtained was because the application was used for priority purposes for United Kingdom Application GB8320518, issued as GB2127401. (Id.)

could be difficult to detect crystalline material even when it constitutes 15% of the sample. (Lancaster Decl. ¶ 7.) These observations find contemporaneous support in a report prepared by Glaxo in 1983 concluding that the Debye-Scherrer method of detection is very useful when sufficient crystalline material is present, specifically in percentages greater than 10%. (Lancaster Decl. Ex. D: Methods of Detection of Crystalline Material in Amorphous Cefuroxime E47 Ether and Characterization of Its Diastereoisomeric Polymorpha dated 11-3-83 ("Detection Report") at 3.) The report also indicated that the smallest amount of crystalline material detectable was 10%. (Id. at 5.)[9]

The Court accepts the observations of the report and the statements of Dr. Lancaster.[10] This information, by explaining

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[9] In oral argument, Ranbaxy's counsel pointed out that the report in two places refers to the detection of crystalline material constituting 5% of the sample. (Detection Report at 3, 6.)

[10] At oral argument, Ranbaxy's counsel did call into question these materials. For instance, counsel questioned whether the experiment in the report used up-to-date X-ray equipment, noted that Lancaster did not apparently write the report or invent the product in question, and doubted the completeness of the submission. But most importantly, he contended that these materials are inadmissible extrinsic evidence. While these materials do appear to be extrinsic to the '181 patent and its history, see, e.g., Vitronics Corp., 90 F.3d at 732 (stating that expert testimony is extrinsic), courts do permit consideration of expert technical testimony as an aid to the court in understanding the technology involved and in reaching a conclusion as to how individuals skilled in the art would interpret the language in the claim, see, e.g., Tanabe Seiyaku Co., 109 F.3d at 732; Fonar Corp. v. Johnson & Johnson, 821 F.2d 627, 631 (Fed Cir. 1987), rejected on other grounds by

the test referred to in the United Kingdom patent definition, calls into serious doubt Ranbaxy's contention that claim 1 only applies to cefuroxime axetil containing extremely minute amounts of crystalline material, for instance, less than 1%. (Def.'s Mem. at 11.) While the United Kingdom patent definition does perhaps favor a more restrictive interpretation of the claim, the practicalities of the X-ray crystallography test, taken together with the common meaning of "essentially," do not call into serious question our conclusion that the claim embraces crystalline cefurxime axetil that does not materially alter the characteristics of the invention. The X-ray test's inability to detect crystalline material below 10%, and possibly even 15% in some cases, indicates that, in the words of the United Kingdom patent, "zero for all practical purposes" is actually a number just below 10% and perhaps even just below 15%. A person versed in the art would therefore conclude that a level between 10% to 15% is, "for all practical purposes," essentially free of crystalline material.

Ranbaxy's other major argument depends on the prosecution history of the '181 patent itself. The company argues that

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Cardinal Chem. Co. v. Morton Int'l, Inc., 113 S. Ct. 1967 (1993). Because the British patent application definition urged by Ranbaxy relies so heavily on the capabilities of X-ray crystallography, it is useful and perhaps even necessary for the Court to consider other evidence bearing on these capabilities in order to understand and interpret the definition in light of the knowledge of one with ordinary skill in the field.

Glaxo's failure to obtain approval of the supposedly broader original claim 1 describing cefuroxime axetil "in highly pure substantially amorphous form" and its subsequent substitution of the originally dependent and therefore narrower original claim 4 covering cefuroxime axetil "essentially free from crystalline material" demonstrates the narrowness of the issued claim 1. (Def.'s Mem. at 10-14.) Ranbaxy also emphasizes that the application contains a statement that the cefuroxime axetil ester "is preferably essentially free from crystalline material," indicating that this language is narrower than the rejected "highly pure, substantially amorphous" language. (Def.'s Mem. at 10.)

These arguments ultimately fail because they read too much into the prosecution history of the claims. The rejection was apparently based on indefiniteness grounds and not an express concern that the application language claimed excessive percentages of crystalline cefuroxime axetil. (Prosecution History at 90.) The amendments undertaken after the first rejection resolved any lack of definiteness as to the relative quantities of crystalline and amorphous materials because the phrase "essentially free from crystalline material" was never amended. (Prosecution History at 105.) In fact, much of the prosecution history relates, not to the description, but to the different and apparently irrelevant question of whether the

claimed invention was obvious in light of prior art.[11] (Prosecution History at 90-91, 108-21, 123-24, 130-41.)

Ranbaxy's attempt to use the examples and the statements in the specification also fails to show that the ordinary meaning of the phrase "essentially free from crystalline material" should be abandoned. Ranbaxy simply tries to prove too much from the words used in the specification of patent '181. Ranbaxy argues that Examples 22 and 26 of the specification are instances of "highly pure, substantially amorphous" cefuroxime axetil while Examples 18 and 21 are examples of the narrower "essentially free from crystalline material" category. (Def.'s Mem. at 11.) The latter two examples supposedly fall under the narrower category because Example 18 states that X-ray powder analysis showed a few faint lines suggesting the presence of a few crystals and Example 21 describes cefuroxime axetil containing "<1% crystalline material" upon microscopic examination. (Id.) Examples 22 and 26, however, supposedly describe "substantially amorphous" cefuroxime axetil. (Id.) Based on admissions made by Glaxo in prosecution of two other patents, Ranbaxy contends that Example 22 involved a sample containing "approximately 10% crystalline material."[12] (Id; Zimmerman Decl. Ex. 12: Prosecution History of United

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[11] Counsel for Ranbaxy conceded at oral argument that it is not litigating the prior art rejection.

[12] Glaxo appears to agree in its brief that Example 22 contains 10% crystalline cefuroxime axetil. (Pl.'s Mem. at 4.

States Patent No. 4,994,567 at 3 ("Example 22 of the specification has shown that the product contains approximately 10% crystalline material."); Ex. 13: United States Patent No. 5,013,833 at col. 10, lines 20-39 (providing same Example 22 as '181 Patent); Ex. 14: Prosecution History of United States Patent No. 5,013,833 at 3 ("For example, Example 22 of applicants' specification has been shown to produce a product which contains approximately 10% crystalline material in addition to the amorphous product.")[13]

Given the context of this case, these examples cannot be used to create any distinctions because of the inherent confusion and lack of clarity involved. For instance, Examples 18 and 21 do not even refer to the material as essentially free of crystals. ('181 Patent cols 9-10.) Example 18, because it refers to X-ray analysis ('181 Patent col 9, lines 29), may also be an instance of crystalline material exceeding 10% given the measuring limitations of the X-ray technique discussed above.

Ranbaxy also argues that the Federal Circuit has interpreted the language "essentially free" to mean that a material is present only as an unavoidable impurity. (Def.'s Mem. at 7-8 (citing In re Marosi, 710 F.2d 799 (Fed. Cir. 1983).) The Federal Circuit has also held, however, that the phrase "consisting essentially of" excludes elements that would

materially affect the characteristics of the invention, Water Techs. Corp., 850 F.2d at 666; PPG Indus., Inc. v. Guardian Indus. Corp., 156 F.3d at 1354. It has rejected, based on prosecution history and specification language, the interpretation of the phrase "substantially free of mature lymphoid and myeloid cells" as meaning an immeasurable amount of these cells and instead concluded that the phrase meant no more than 10% of these cells. Johns Hopkins Univ. v. CellPro, Inc., 152 F.3d 1342, 1354-55 (Fed. Cir. 1998). Although none of these cases establish the correct meaning of the phrase in this context, they do indicate that Ranbaxy's cited case does not call this Court's ordinary meaning construction into serious doubt.[14]

The Court therefore construes the "essentially free from crystalline material" phrase as meaning free of crystalline

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[14] Glaxo cites the case of Rohm and Haas Co. v. Lonza Inc., 997 F. Supp. 635 (E.D. Pa. 1998), to support its contention that the "essentially free from crystalline material" phrase excludes only crystalline material which would materially affect the invention. (Pl.'s Mem. at 13.) This case is less than clear because it could be read as interpreting the phrase "substantially free of nitrosamines or precursors" as including within the claim only undetectable nitrosamines or precursors. Rohm and Haas Co., 997 F. Supp. at 640. This interpretation, however, appears different from the interpretation advanced by the prevailing plaintiff, emphasizing whether the content of these materials "is sufficiently low that no appreciable danger to humans or animals will result from contact with the compositions at issue." Id. In any case, the detectability definition, if it was in fact adopted by court, was based on an express definition in the patent specification. Id. As has been discussed above, the United Kingdom patent definition is insufficient to support Ranbaxy's arguments.

cefuroxime axetil that materially detracts from or affects the characteristics of the claimed invention.[15]

Once the claim construction aspect of the infringement inquiry is performed, the next step in analyzing a claim of literal infringement requires that the properly interpreted claims be compared to the accused product or device. Southwall Tech., Inc. v. Cardinal IG Co., 54 F.3d 1570, 1575 (Fed. Cir. 1995). The determination of whether the properly construed

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[15] Ranbaxy also appears to argue that Glaxo's opposition to Ranbaxy's ANDA contains some form of admission. (Def.'s Mem. at 14 n.6.) Glaxo did file a petition with the FDA challenging the approval of an ANDA on the grounds that:

> [A]n ANDA for a product formulated wholly or partially with the crystalline form of cefuroxime axetil would violate governing law for at least two reasons: 1) failure to satisfy the requirement that an ANDA drug contain the same active ingredient as the reference listed drug and 2) failure to satisfy the requirement that the ANDA drug have the same labeling as the innovator product.

(Zimmerman Decl. Ex. 9: Citizen Petition at 4.) This petition does not alter the Court's interpretation of the claim language, largely because it does not stress the actual meaning of the '181 claims in question.

Because prosecution estoppel does not technically apply to cases of literal infringement, see, e.g., Biodex Corp., 946 F.2d at 862-63, the very recent Federal Circuit decision in Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., No. 95-1066, 2000 WL 175346 (Fed. Cir. Nov. 29, 2000) does not mandate a different result. The Court also notes that it does not appear that Glaxo's amendment satisfies the requirements for a "narrowing amendment," which the Festo Corp. court held precludes the application of the doctrine of equivalents. Id. at *3, *28-*[illegible]

claims read on the accused device is typically a question of fact. Id. In order to make out a successful infringement action, the patentee must show that the defendant's product satisfies every limitation of a claim. Strattec Sec. Corp. v. General Auto. Speciality Co., 126 F.3d 1411, 1418 (Fed. Cir. 1997). Because of the special drug infringement requirements of 35 U.S.C. § 271, the court must focus on the admittedly non-existent product that is likely to be sold after FDA approval, although the contents of the ANDA are certainly very relevant to this inquiry. Glaxo, Inc. v. Novopharm, Ltd., 110 F.3d 1562, 1568 (Fed. Cir. 1997).[16] In this case, the Court finds that plaintiff has made an adequate showing of likelihood of success on its claim that Ranbaxy's likely product infringes claim 1 of the '181 patent.

Claim 1 of patent '181 provides for:

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[16] Neither party refers to this special requirement. But, because the Court's decision still relies heavily on the ANDA information, it does not believe that the use of this "likely product" terminology is particularly significant.

The Court also notes that there appears to be a restriction concerning which materials may be considered, with the Federal Circuit recently holding that information concerning the biobatch actually tested during the ANDA process often cannot be considered in the "likely product" inquiry. Bayer AG v. Elan Pharm. Research Corp., 212 F.3d 1241, 1249-50 (Fed. Cir. 2000). Because neither party has addressed this issue and both cite the same types of materials, the Court will not restrict its analysis to any particular items.

> Cefuroxime axetil in amorphous form essentially free from crystalline material, and having a purity of at least 95% aside from residual solvents.

('181 Patent col. 13, lines 4-6.) There is no doubt that Ranbaxy's ANDA seeks to use cefuroxime axetil as an active ingredient in doses of 125 mg, 250 mg, and 500 mg. (ANDA Vol. 1 at R03771.) The basic chemical item, cefuroxime axetil, is therefore the same as in the claim. The medication is also in tablet form for oral administration and is intended to combat bacterial infections. (Id. at R03768-R03771.) Furthermore, the proposed medication contains between 0.32% and 2.0% related impurities, excluding residual solvents. (Drug Master File at R04849). The Court therefore finds that the solvent limitation has been fulfilled. In fact, Ranbaxy does not appear to address these components in a significant fashion, and it instead focuses on the "essentially free from crystalline material" limitation. (Def.'s Mem. at 15-16.)

Under the interpretation adopted above, the Court concludes for purposes of this preliminary injunction application that the proposed medication contains cefuroxime axetil "essentially free from crystalline material." The Court reaches this conclusion because it finds that the level of crystalline cefuroxime axetil in Ranbaxy's likely product does not materially affect the characteristics of the cefuroxime axetil, specifically its bioavailability. Ranbaxy's proposed product contains a mixture

of 12% crystalline cefuroxime axetil and 88% amorphous cefuroxime axetil. (Ranbaxy's Fax Amendment at R5965, R5969; ANDA Application at R-3915-R03917; Ternyik Decl. ¶ 5.) The ANDA permits the content of crystalline cefuroxime axetil to be no more than 15% and no less than 10% of the total amount of cefuroxime axetil. (Ranbaxy's Fax Amendment at R5962, R5988-R5993.) While this crystalline material is an active ingredient of the product, delivering cefuroxime to the patient (Ternyik Decl. ¶ 6), the presence of this level of crystalline material does not actually impair the drug's bioequivalency. In the words of Ranbaxy's Fax Amendment:

> Ranbaxy's dissolution and stability testing establishes that the percentage of crystalline and amorphous forms in its tablets (12% and 88%, respectively) does not adversely affect the identity, strength, quality, purity, potency and performance of the drug product . . . . In particular, the percentage of crystalline component in Ranbaxy's tablets shows no adverse impact on the solubility or in-vivo characteristics of the drug product, since the drug product complies with the bioequivalence criteria.

(Ranbaxy's Fax Amendment R5969.) The Court finds that statement constitutes an admission on the part of Ranbaxy. See, e.g., U.S. Surgical Corp. v. Hosp. Prods. Int'l, 701 F. Supp. 314, 347 (D. Conn. 1988) (finding FDA submissions by defendants to be admissions); Merck & Co. v. Danbury Pharm., Inc., 694 F. Supp. 1, 21 (D. Del. 1988) (considering patentee's FDA submission), aff'd, 873 F.2d 1418, 1420 (Fed. Cir. 1989). It therefore demonstrates

that Ranbaxy's likely product falls under the essentially free of crystalline material language. Because Ranbaxy's likely product therefore satisfies every limitation of claim 1, this Court finds a reasonable probability of success of plaintiff's claim of literal infringement of claim 1 of the '181 patent.[17]

II. Irreparable Harm

The Court finds that Glaxo will be irreparably harmed if a preliminary injunction is not granted. Glaxo's showing of likely infringement, coupled with the absence of a substantial challenge to the '181 patent's validity, gives rise to a presumption of irreparable harm. Courts have found that a rebuttable presumption of irreparable harm arises on a clear showing of patent validity and infringement. See, e.g., Roper Corp. v. Litton Sys., Inc., 757 F.2d 1266, 1271 (Fed. Cir. 1985); Smith Int'l, Inc. v. Hughes Tool Co., 718 F.2d 1573, 1581 (Fed. Cir. 1983). This presumption arises even if the issue of validity is

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[17] Because of our resolution of the patent infringement claim as to claim 1 of the '181 patent, the Court does not have to consider any possible infringement of claims 2 through 5, 7 through 11, 13, and 14. In fact, neither party really briefed the issue of the infringement of these claims, although Glaxo did submit a claim chart listing each claim and the evidence supporting a conclusion of infringement. (Pl.'s App. Ex. I: Claim Chart at 1-3.)

The Court also does not have to consider whether Ranbaxy's likely product infringes the '181 patent under the doctrine of equivalents. If it needed to do so, it most likely would have concluded that it would infringe the '181 patent under this doctrine as well.

not raised due to the alleged infringer's failure to challenge it. Roper Corp., 757 F.2d at 1272 (finding that district court erred when it held that plaintiff had not made strong showing of validity when defendant did not even challenge validity); see also 3M Unitek Corp. v. Ormco Co., 96 F. Supp. 2d 1042, 1046 (C.D. Cal. 2000) (stating that if defendant fails to identify any persuasive evidence raising substantial question of validity, existence of patent satisfies patentee's burden). Because the Court has found that Glaxo has clearly shown infringement of the '181 patent and, in the words of Ranbaxy's own brief, "Ranbaxy has not challenged the validity of the '181 patent in [its] Opposition" (Def.'s Mem. at 21 n.10), the Court will apply this presumption of irreparable harm. Even in the absence of a presumption, the Court still finds that Glaxo sufficiently demonstrates irreparable harm from Ranbaxy's infringement.

In considering whether the presumption has been rebutted, a court may consider such factors as the patent owner's market share, any delay on the part of the patent owner in bringing suit indicating that it does not believe it suffered irreparable harm, Polymer Tech., Inc. v. Bridwell H.A., 103 F.3d 970, 974 (Fed. Cir. 1996), and any licensing by the patentee demonstrating that it believes a royalty would be adequate compensation, id. After consideration of these factors and the other matters raised by

the parties, the Court concludes that irreparable harm exists in this case.

Rivera, a senior product manager at Glaxo Wellcome, declared that Glaxo's Ceftin® tablet sales exceed[ ]annually in the United States, that it sold[ ]of Ceftin® last year worldwide, and that its total Ceftin® sales in the United States since 1988 have been in excess of[ ] (Rivera Decl. ¶¶ 1, 4.) The Court accepts these figures and also finds that, although Ranbaxy contests these figures with its own declarations and other evidence (see Def.'s Mem. at 22), Glaxo has sufficiently demonstrated that, facing any generic competition, it will lose[ ]in sales and[ ]of its market share in the first three months,[ ]between the third and sixth months and[ ]of its market share by the end of six months, and [ ]between the sixth and twelfth months and[ ]of its market share. (Rivera Decl. ¶ 13.) It therefore may lose[ ]in sales during the first year of infringement. (Id.) It also may lose approximately[ ]in sales during the remaining life of the '181 patent, which expires on July 28, 2003. (Id. ¶ 14.) In the face of these numbers, Ranbaxy admits that Ranbaxy Laboratories Limited, which will answer for any damages against Ranbaxy (Def.'s Mem. at 22 n.12), is worth only $350 million, not including the expected first year profit of $25 million from the sale of cefuroxime axetil (id. at 22 (citing

Chattaraj Decl. ¶ 8). This amount appears inadequate to compensate Glaxo, and, even if it were sufficient, does not automatically negate a showing of irreparable harm. See, e.g., Roper Corp., 757 F.2d at 1269 n.2; Atlas Powder Co. v. Ireco Chems., 773 F.2d 1230, 1233 (Fed. Cir. 1985); 3M Unitek Corp., 96 F. Supp. 2d at 1051.

The Court also finds that Glaxo acted promptly in bringing this suit against Ranbaxy. Its in-house intellectual property counsel apparently wrote a letter to Ranbaxy on April 20, 2000 concerning any possible infringement of Glaxo's cefuroxime axetil patents (Zimmerman Decl. Ex 20: Letter from David J. Levy dated 4-20-00), and a further letter dated September 25, 2000 seeking more information (id. Letter from David J. Levy to Darrell L. Olson, Esq., dated 7-28-00). Glaxo's litigation counsel wrote a similar letter dated September 25, 2000. (Id. Letter from Stephen B. Judlowe, Esq., to Darrell L. Olson, Esq., dated 9-25-00.) In response to information received on October 16, 2000 that Ranbaxy was expecting FDA approval in November of 2000 (Pls.' App. Ex E: James Matthews, Bayer to Pump $5 million in Ranbaxy, Economic Times, Oct. 13, 2000, available at http://www.economictimes.com/today/13comp06.htm.), Glaxo filed its Complaint on October 20, 2000 (Compl.). Not only did Glaxo react promptly to Ranbaxy's conduct, but it also filed a Complaint in the United States District Court for the Northern

District of Illinois against Apotex Inc. seeking injunctive and other relief for infringement of the '181 patent. (Zimmerman Decl. Ex. 28: Compl. docketed 9-22-00 ¶¶ 6-14.)

Ranbaxy contends inter alia that no irreparable damages exist because any economic loss is speculative and not immediate given the absence of the necessary FDA approval, Glaxo has given its rights to market, sell and distribute Ceftin® to Professional Detailing, and any claim of irreparable harm must be viewed in light of Glaxo's lengthy period of exclusivity. (Def.'s Mem. at 21-24.) See, e.g., Cordis Corp. v. Medtronic, Inc., 780 F.2d 991, 996 (Fed. Cir. 1985) ("A preliminary injunction will not issue simply to prevent a mere possibility of injury, even where prospective injury is great." (quoting S.J. Stile Assocs., Ltd. v. Snyder, 646 F.2d 522, 525 (C.C.P.A. 1981))). The Court, however, rejects these arguments. Admittedly, the FDA apparently has not approved Ranbaxy's ANDA and therefore the company cannot launch its cefuroxime axetil product yet. (Chattaraj Decl. ¶ 8; Ternyik Decl. ¶ 3.) Chattaraj also claimed that the timing of the approval could not be determined (Chattaraj Decl. ¶ 4), that Ranbaxy would need at most forty-five days to manufacture the necessary quantity of products for a launch, that it has ceased manufacturing, and has not contacted distributors, established a price list, or prepared any marketing material (Chattaraj Dep. at 46-61). Chattaraj,

however, also stated that he has told customers that FDA approval could come "any day now." (Id. at 61.) The Court therefore concludes that sufficient immediacy exists given the context of this case. Furthermore, the mere fact that Glaxo has contracted to give Professional Detailing exclusive marketing, sales, and distribution rights, while continuing to manufacture the product, does not indicate that monetary damages are sufficient.

III. The Balance of Hardships

The Court finds that the balance of hardship generally favors Glaxo, although it does appear that Ranbaxy faces certain hardships if a preliminary injunction is granted. An injunction should ordinarily not be granted if its impact on the party enjoined would be more severe than the injury the moving party would suffer if it were not granted. Litton Sys, Inc. v. Sundstand Corp., 750 F.2d 952-60 (Fed. Cir. 1984). The proximity of patent expiration is not a factor to be considered. Atlas Powder Co. v. Ireco Chems., 773 F.3d 1230, 1234 (Fed. Cir. 1985) ("Patent rights do not peter out as the end of the patent term, usually 17 years, is approachable.") As Ranbaxy admits (Def.'s Mem. at 25), the moving party's satisfaction of the likelihood of success factor must be considered under this balancing factor of the test. Illinois Tool Works, Inc. v. Grip-Pak, Inc., 906 F.2d at 683, 679 (Fed. Cir. 1990).

The Court finds that Glaxo demonstrates that the balance of hardships tips, perhaps just slightly, in its favor. The advantages of being the first generic supplier of a product, though perhaps not without weight, cannot overcome the clear harm to Glaxo's intellectual property rights as well as its market share and sales of Ceftin®. Cf. Atlas Powder Co., 906 F.2d at 1234 (issuing preliminary injunction even though patent had only a year to run and injunction affected two-thirds of defendant's sales and would result in layoff of 200 employees). The Court also notes that Ranbaxy has not shown that any other generic manufacturer has entered the cefuroxime axetil market.[18] The Court therefore concludes that Glaxo has satisfied the balance of hardships factor.

IV. The Public Interest

The Court finds that a grant of a preliminary injunction favors the public interest. Both the public interest and the possibility of harm to others are factors to be considered in the preliminary injunction inquiry. Smith Int'l, Inc. v. Hughes Tool Co., 718 F.2d 1573, 1579 (Fed. Cir. 1983). In some cases, a more important public interest may prevent the issuance of an injunction. Hybritech, Inc. v. Abbot Labs., 849 F. 2d 1446, 1458

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[18] Ranbaxy refers to the ANDA application of Apotex Inc. (Def.'s Mem. at 26.) But its only reference is to a Complaint, almost identical to the Complaint filed in this case, of Glaxo against Apotex Inc. (Zimmerman Decl. Ex. 28: Compl. docketed 1-22-00.)

(Fed. Cir. 1988). Generally, however, "no public interest is served by allowing patent infringement." A.K. Stamping Co. v. Instrument Specialities Co., 106 F. Supp. 2d 627, 656 (D.N.J. 2000) (citations omitted). Considerations, such as the possibility of a lower price, are not grounds for infringing a patent. Payless Shoesource, Inc. v. Reebok Int'l Ltd., 998 F.2d 985, 991 (Fed. Cir. 1993).

Glaxo has clearly established a substantial likelihood of success on the merits by demonstrating that Ranbaxy's proposed product most likely literally infringes its '181 patent, and it therefore appears that public interest considerations favor protection of its property rights. Ranbaxy claims that the public is entitled, under the compromise established by the ANDA process permitting extension of patent terms for patent holders and expedited approval proceedings for generic manufacturers, to competition in the cefuroxime axetil market and lower priced cefuroxime axetil. (Def.'s Mem. at 26-27.) This argument, however, cannot justify an infringement of intellectual property rights. In particular, it appears similar to the prohibited argument that injunctive relief is required to enable the public to buy less expensive products. Payless Shoesource, Inc., 750 F.2d at 991. In the end, Ranbaxy's asserted public interest does not outweigh the fact that its product will likely infringe Glaxo's patent.

CONCLUSION

Glaxo establishes the requirements for a preliminary injunction enjoining Ranbaxy from launching any cefuroxime axetil product under ANDA No. 65-043. The Court will file an order entering the injunction after determining the size of the bond required by Federal Rule of Civil Procedure 65(c) or whether the order should be made final, thereby obviating the need for a bond. The Court issues an Order to Show Cause directing the parties to address these two subjects.

IT IS THEREFORE on this 18th day of December, 2000 **ORDERED** that defendant shall **SHOW CAUSE** on February 5, 2001, as to (1) the amount of bond that should be required pursuant to Federal Rule of Civil Procedure 65(c), and (2) whether the preliminary injunction should be made final, thereby obviating the need for the posting of a bond; and

IT IS FURTHER ORDERED that defendant shall submit any response to said Order to Show Cause on or before January 12, 2001; and

IT IS FURTHER ORDERED that plaintiffs shall file any response to defendant's submission on or before January 22, 2001; and

IT IS FURTHER ORDERED that defendant shall file any reply to plaintiffs' submission on or before February 1, 2001.

Mary L. Cooper

MARY L. COOPER
United States District Judge

United States Patent [19]

Crisp et al.

[11] Patent Number: 4,562,181

[45] Date of Patent: Dec. 31, 1985

[54] AMORPHOUS FORM OF CEFUROXIME ESTER

[75] Inventors: Harold A. Crisp, Harrow Weald; John C. Clayton, Pinner, both of England

[73] Assignee: Glaxo Group Limited, London, England

[21] Appl. No.: 518,693

[22] Filed: Jul. 29, 1983

[30] Foreign Application Priority Data

Jul. 30, 1982 [GB] United Kingdom 8222019

[51] Int. Cl.⁴ A61K 31/545; C07D 501/24

[52] U.S. Cl. 514/202; 544/22

[58] Field of Search 544/22; 424/246; 514/202

[56] References Cited

U.S. PATENT DOCUMENTS

4,267,320	5/1981	Gregson et al.	424/246
4,444,686	4/1984	Jasys	260/239.1

FOREIGN PATENT DOCUMENTS

1572993	8/1980	United Kingdom .
1598568	9/1981	United Kingdom .

OTHER PUBLICATIONS

Sato et al, Chem. Pharm. Bull., 29(9), 2675-2682 (1981).
Masters et al, "Aseptic and Closed Cycle Spray Drying in Pharmaceutical/Biochemicals Manufacture", in Process Biochemistry, Jan./Feb., 1975.
Ripple, "Remingtons Pharmaceutical Sciences", Chap. 88, pp. 1535-1552.

Primary Examiner—Donald G. Daus
Assistant Examiner—Robert Benson
Attorney, Agent, or Firm—Bacon & Thomas

[57] ABSTRACT

There is described a product which is a highly pure substantially amorphous form of cefuroxime axetil (cefuroxime 1-acetoxyethyl ester) which is stable, which has increased absorption via the gastro-intestinal tract and has a correspondingly high level of bioavailability on oral or rectal administration.

Methods of preparing the product are also described which involve the recovery of the product from a solution thereof. A preferred method is the use of spray drying techniques, though roller drying, solvent precipitation or freeze-drying are also described.

Also disclosed are pharmaceutical compositions containing the product and methods for its use in medicine.

14 Claims, 2 Drawing Figures

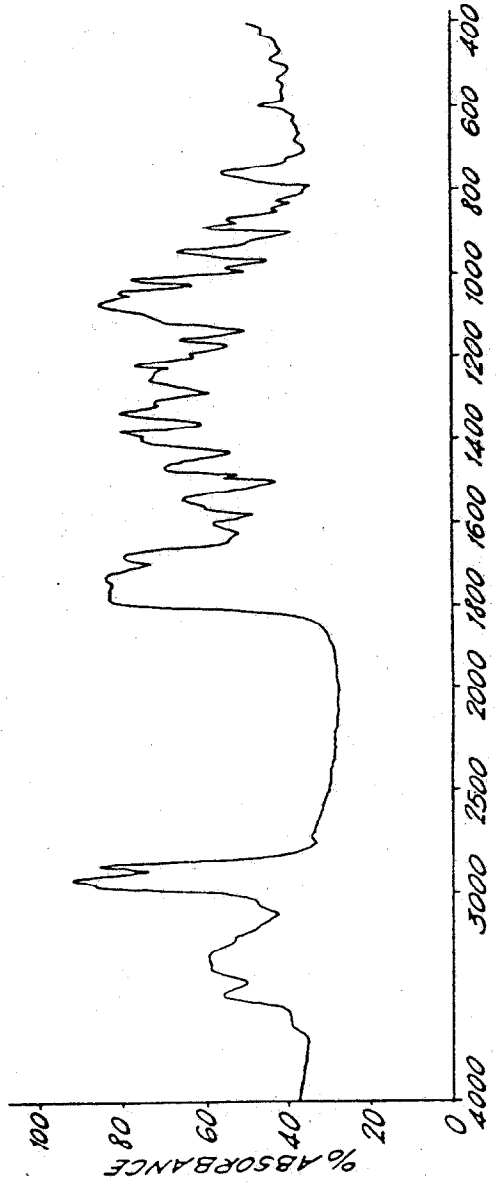
100
80
60
40
20
0
% ABSORBANCE
4000
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
WAVENUMBER (CM⁻¹)

FIG.1.

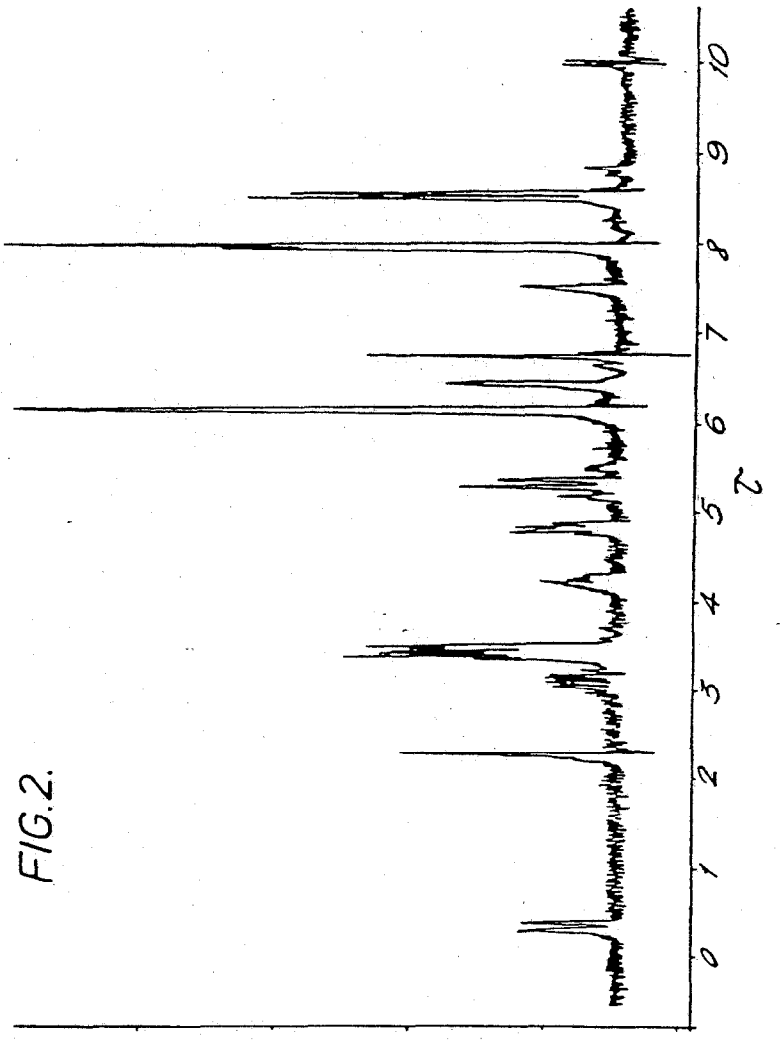

FIG. 2.

AMORPHOUS FORM OF CEFUROXIME ESTER

This invention relates to a novel, amorphous form of the 1-acetoxyethyl ester of cefuroxime(cefuroxime axetil), to a process for the preparation thereof, to a composition containing it and to its use in medicine.

The compound (6R,7R)-3-carbamoyloxymethyl-7-[(Z)-2-(fur-2-yl)-2-methoxyiminoacetamido]ceph-3-em-4-carboxylic acid has the approved name "cefuroxime". This compound is a valuable antibiotic characterised by high broad spectrum activity against gram-positive and gram-negative microorganisms, this property being enhanced by the very high stability of the compound to β-lactamases produced by a range of gram-positive and gram-negative microorganisms. It is well tolerated in the mammalian body and is used widely as an antibiotic in clinical practice. Cefuroxime and its salts are principally of value as injectable antibiotics since they are poorly absorbed from the gastro-intestinal tract and are therefore present in sera and urine only in low concentrations after oral administration. There has accordingly been a need for a form of cefuroxime which is capable of being absorbed from the gastrointestinal tract following oral administration.

We have found that appropriate esterification of the carboxyl group of cefuroxime improves the effectiveness on oral administration. The presence of such an appropriate esterifying group results in significant absorption of the compound from the gastro-intestinal tract, whereupon the esterifying group is hydrolysed by enzymes present in, for example, serum and body tissues to yield the antibiotically active parent acid. To be effective upon oral administration the ester must be stable enough to reach the site of absorption without significant degradation, must be sufficiently absorbed upon reaching the appropriate site, and must be sufficiently susceptible to hydrolysis by systemic esterases for the parent acid to be liberated within a short time of the ester being absorbed. British Patent Specification No. 1571683 (U.S. Pat. No. 4,267,320) discloses and claims a number of esters of cefuroxime as having properties rendering them of significant potential value as orally administrable antibiotics.

It is important that cephalosporin compounds for oral administration should be in a form which provides high bioavailability whereby absorption of the antibiotic into the blood stream is maximised and the amount of the antibiotic remaining in the gastro-intestinal tract is minimised. Any antibiotic which is not absorbed will be therapeutically ineffective and also, by remaining in the gastro-intestinal tract, may cause side effects. Other factors in addition to bioavailability are also of importance including in particular the need for the cephalosporin compound to be in a substantially pure form which is stable upon storage. In general it has hitherto been found that cephalosporin compounds in highly pure crystalline form provide the best balance of properties, such materials having good stability upon storage as well as high bioavailability upon administration.

Of the esters described in British Patent Specification No. 1571683, we have found cefuroxime axetil to be of particular interest. The processes for the preparation of the above ester exemplified in British Patent Specification No. 1571683 produce the material either in relatively impure amorphous form or in the form of purer crystalline material

In view of past experience in the cephalosporin field, we first prepared cefuroxime axetil for commercial evaluation in substantially pure, crystalline form. We have however surprisingly found that substantially pure, crystalline cefuroxime axetil does not have the best balance of properties for commercial use and that, contrary to previous experience in the cephalosporin field, cefuroxime axetil is advantageously used in a highly pure, substantially amorphous form. We have thus established that highly pure cefuroxime axetil when in substantially amorphous form has higher bioavailability upon oral administration than when in crystalline form and that moreover the amorphous form of cefuroxime axetil has adequate chemical stability upon storage. This is despite the known tendency for amorphous materials to have inferior chemical stability to crystalline materials and also the known tendency for highly pure amorphous materials to crystallise. Thus, unlike previous cephalosporin compounds which have been developed for commercialisation, cefuroxime axetil is advantageously prepared and used in highly pure amorphous form rather than in crystalline form.

According to one aspect of the present invention, there is provided cefuroxime axetil in highly pure, substantially amorphous form.

The cefuroxime axetil in accordance with the invention preferably contains less than 5% mass/mass (m/m), advantageously less than 3% m/m, of impurities. It is to be understood that references herein to 'impurities' are to be understood as not including residual solvents remaining from the process used in the preparation of the cefuroxime axetil of the invention. Any residual solvent present will desirably only be present in less than 6% m/m and most preferably less than 2% m/m.

Typical impurities which may be present are the Δ^2-isomers of cefuroxime axetil and the corresponding E-isomers of cefuroxime axetil.

The cefuroxime axetil ester in accordance with the invention is preferably essentially free from crystalline material.

Cefuroxime axetil possesses an asymmetric carbon atom at the 1-position of the 1-acetoxyethyl group and can therefore exist in the form of R and S isomers and mixtures thereof. The amorphous cefuroxime axetil ester according to the invention is preferably in the form of a mixture of its R and S isomers, such a mixture having a substantially improved solubility as compared with amorphous R isomer or amorphous S isomer alone. The mole ratio of R isomer to S isomer may for example be within the range of 3:2 to 2:3 with ratios of 1.1:1 to 0.9:1, particularly about 1:1, being preferred.

The cefuroxime axetil of the invention desirably has an $E_1\,cm^{1}\%$ at its λ_{max} in methanol, when corrected for any solvent content, of from about 395 to 415. In addition, the cefuroxime axetil of the invention having an R to S isomer ratio of from 0.9:1 to 1.1:1, particularly of about 1:1 desirably has an $[\alpha]_D$ value in dioxan of from about +35° to +41°, again when corrected for any solvent content. FIGS. 1 and 2 of the accompanying drawings are respectively infra-red and n.m.r. spectra for specimens of highly pure, substantially amorphous cefuroxime axetil in accordance with the invention.

After absorption cefuroxime axetil is converted into the parent antibiotic acid cefuroxime which is known to exhibit high antibacterial activity against a broad range of gram-positive and gram-negative organisms. Cefuroxime axetil is thus useful in the oral or rectal treatment

of a variety of diseases or infections caused by pathogenic bacteria.

The cefuroxime axetil according to the invention is conveniently prepared by a process which constitutes a further feature of the present invention and which comprises recovering cefuroxime axetil from a solution thereof under conditions whereby a highly pure, substantially amorphous product is obtained.

Techniques which may be employed to recover substantially amorphous cefuroxime axetil from the solution thereof include those wherein solvent is removed from the solution, preferably rapidly, and the product deposited and those wherein the product is precipitated from solution. Methods involving the use of these procedures which have been found satisfactory include spray drying, roller drying, solvent precipitation and freeze drying.

Solvents for cefuroxime axetil will be chosen according to the technique and conditions to be employed. Suitable solvents for dissolving cefuroxime axetil to form solutions from which recovery is enabled include organic solvents, for example ketones, e.g. acetone; alcohols, e.g. methanol or ethanol, if desired in the form of methylated spirits (e.g. IMS); acetonitrile; tetrahydrofuran; dioxan; esters, e.g. methyl or ethyl acetate; chlorinated solvents e.g. dichloromethane or chloroform; and mixtures thereof, if desired with other solvents, e.g. water, where this gives a homogeneous phase.

The concentration of cefuroxime axetil in the solvent is with advantage as high as possible, commensurate with a substantially amorphous product being obtained, preferred concentrations being greater than 1% m/m, preferably greater than 10% m/m. The maximum concentration of the cefuroxime axetil in the solvent will depend upon the solvent used and in general will be less than 30% m/m. For example, the concentration of cefuroxime axetil in acetone will conveniently lie within the range 10 to 20% m/m. The solvents may if desired be heated as an aid to solubility and removal of solvent.

In general, we have found that the cefuroxime axetil has sufficient heat stability to withstand spray drying and accordingly spray drying is a preferred method of effecting recovery. Spray drying systems can be operated in known manner to obtain an amorphous product essentially free from crystalline material and free from particulate contaminants. Closed cycle spray drying systems in which the drying medium is recycled are particularly safe and economic for use in obtaining the product of the present invention.

When employing spray drying, suitable solvents for dissolving cefuroxime axetil prior to spray drying include organic solvents, for example ketones, e.g. acetone; alcohols, e.g. methanol or ethanol, if desired in the form of methylated spirits (e.g. IMS); acetonitrile; tetrahydrofuran; esters, e.g. methyl or ethyl acetate; chlorinated solvents e.g. dichloromethane or chloroform; and mixtures thereof, if desired with other solvents, e.g. water, where this gives a homogeneous phase.

The drying gas can be air but this is undesirable with flammable solvents, inert gases such as nitrogen, argon and carbon dioxide being preferred in this case. The gas inlet temperature to the spray dryer will be chosen according to the solvent used, but may for example be in the range 50°–140° C. preferably 60°–125° C. The gas outlet temperature is similarly dependent on the solvent but may for example be in the range 45°–100° C., preferably 50°–80° C.

The use of rapid evaporation techniques, in particular the use of spray drying also leads particularly readily to the formation, under appropriate conditions, of products having a consistent range of particle sizes. The product from spray drying has the form of hollow microspheres which can conveniently be compounded into pharmaceutical compositions.

When employing roller drying, suitable solvents for dissolving the cefuroxime axetil prior to drying include ketones, e.g. acetone; alcohols, e.g. methanol or ethanol, if desired in the form of methylated spirits (e.g. IMS); acetonitrile; tetrahydrofuran; dioxan; esters, e.g. methyl or ethyl acetate; chlorinated solvents e.g. dichloromethane or chloroform; and mixtures thereof, if desired with other solvents, e.g. water, where this gives a homogeneous phase.

In carrying out the above spray- or roller-drying techniques, it is highly desirable that the boiling point of the solvent employed will lie below the coagulation point of the product of the invention under the conditions used. In general, the boiling point of the solvent will preferably be below 80° C. unless reduced pressure is employed thereby allowing the use of higher boiling solvents.

When employing solvent precipitation, suitable solvents from which the cefuroxime axetil may be precipitated include ketones, e.g. acetone; alcohols, e.g. methanol or ethanol, if desired in the form of methylated spirits (e.g. IMS); acetonitrile; tetrahydrofuran; dioxan; esters, e.g. methyl or ethyl acetate; chlorinated solvents e.g. dichloromethane or chloroform; and mixtures thereof, if desired with other solvents, e.g. water, where this gives a homogeneous phase. Precipitation may be effected by the addition of appropriate quantities of a non-solvent for the cefuroxime axetil. Suitable non-solvents include water, alkanes and mixtures of alkanes, e.g. hexane or medium boiling range petrol (e.g. 60°–80° C.), ethers, e.g. isopropyl ether, or aromatic hydrocarbons e.g. benzene or toluene. The solvent and non-solvent should be compatible i.e. they should be at least partially miscible and preferably fully miscible. Typical combinations of solvent and non-solvent are dichloromethane/isopropyl ether, ethyl acetate/petrol and acetone/water. The solid should be removed from solution as quickly as possible and dried as quickly as possible to avoid formation of any crystalline material. As an aid to rapid recovery a carrier gas e.g. air may be bubbled through the solution.

The technique of solvent precipitation may usefully be applied to the reaction mixture remaining after an esterification reaction in which the cefuroxime axetil has been formed in order to obtain amorphous cefuroxime axetil directly. This may be achieved by the addition of a solvent e.g. an ester such as ethyl acetate to the reaction mixture followed by the appropriate non-solvent, e.g. petrol.

When employing freeze-drying, suitable solvents for dissolving the cefuroxime axetil prior to drying include dioxan and t-butanol. The temperature at which the recovery will be effected will depend upon the freezing point of the solvent employed e.g. with dioxan recovery will be effected at a temperature of about 12° C.

In order to obtain cefuroxime axetil ester in highly pure form by the above techniques it is necessary to employ a starting material of suitable purity—i.e. at least as pure as the final product. Such a starting material may be obtained by any convenient method, e.g. by crystallisation.

The solution from which the cefuroxime axetil is recovered preferably contains a mixture of both R- and S-isomers, whereby the product is obtained as a mixture of R- and S-isomers. In general, the R/S isomer ratio of the product in solution is exactly reflected in the final product obtained e.g. by spray drying, and this ratio for the final product can accordingly be controlled if desired by adjustment of the R/S isomer ratio in the solution.

Residual solvent may be present in the final product in varying amounts immediately after evaporation or precipitation. This can if necessary be removed by further treatment, e.g. by drying under vacuum.

The cefuroxime axetil ester according to the invention may be formulated for oral (including buccal) or rectal administration.

Compositions for oral administration are preferred whereby the enhanced absorption of the ester via the gastro-intestinal tract can be utilized. Such pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents e.g. pregelatinised maize starch, polyvinyl-pyrrolidone or hydroxypropyl-methylcellulose; fillers e.g. starch, lactose, micro-crystalline cellulose or calcium phosphates; lubricants e.g. magnesium stearate, hydrogenated vegetable oils, talc, silica, polyethyleneglycols; disintegrants e.g. potato starch or sodium starch glycolate; or wetting agents e.g. sodium lauryl sulphate. Flow aids e.g. silicon dioxide may also be used if desired. The tablets may be coated by methods well known in the art.

The preparation of a composition suitable for forming into tablets, capsules or granules may also be achieved by spray-drying or roller drying a suspension of pure amorphous cefuroxime axetil with the excipients appropriate for the said tablets, capsules or granules.

Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product either for constitution with water or other suitable vehicle before use for administration as a liquid, or for direct administration and then washed down with water or other suitable liquid. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents e.g. sorbitol syrup, methyl cellulose or hydrogenated edible fats and oils such as hydrogenated castor oil; emulsifying or thickening agents e.g. lecithin, aluminium stearates or acacia; non-aqueous vehicles e.g. almond oil, fractionated coconut oil, oily esters or ethyl alcohol; and preservatives e.g. methyl or butyl p-hydroxybenzoates or sorbic acid; and suitable flavouring and sweetening agents.

The cefuroxime axetil of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compositions may contain between 0.1-99% of the active ingredient, conveniently from 30-90% for tablets and capsules and 3-50% for liquid medications. Compositions in dosage unit form conveniently contain 50-500 mg of the active ingredient. Doses employed for human treatment will typically be in the range 100-3000 mg per day, e.g. 1000 to 1500 mg per day for adults and 250 to 1,000 mg per day for children, although the precise dose will depend on, inter alia, the frequency of administration.

In a further aspect therefore the invention provides a pharmaceutical composition comprising cefuroxime axetil in highly pure, substantially amorphous form, in admixture with one or more pharmaceutical carriers and/or excipients. Such compositions are preferably adapted for absorption via the gastrointestinal tract, e.g. for oral administration. In a preferred embodiment, such compositions will desirably include the cefuroxime ester form of the invention essentially free from crystalline material.

In a yet further aspect of the invention, we provide a method of combatting bacterial infections of the human or animal body which comprises administering to the said body orally or rectally an effective amount of a highly pure, substantially amorphous form of cefuroxime axetil.

The following non-limiting Examples illustrate the invention. In all these Examples, the cefuroxime axetil starting materials used were in highly pure crystalline form. Such starting materials may for example be obtained by processes as described in British Pat. No. 1571683, or may alternatively be prepared by the crystallisation of highly pure cefuroxime axetil from an organic solvent, for example an ester such as ethyl acetate in admixture with an ether such as isopropyl ether or an aromatic hydrocarbon such as toluene; or aqueous alcohol, such as industrial methylated spirit. The crystallisation may conveniently be carried out at from 10° to 30° C.

The highly pure sodium cefuroxime which may be used as a starting material for the above esterification process may, inter alia, be obtained by reaction of (6R,7R)-3-hydroxymethyl-7-[(Z)-2-(fur-2-yl)-2-methoxyimino acetamido]ceph-3-em-4-carboxylic acid with chlorosulphonyl isocyanate in an alkyl acetate as solvent at a temperature of from −25° C. to +10° C., followed by hydrolysis in situ at a temperature of +10° to +30° C. and crystallisation by addition of sodium 2-ethylhexanoate in acetone or methyl acetate as solvent.

The preparation of these materials is illustrated in the following Preparations. All temperatures are in °C.

PREPARATION 1

Cefuroxime Sodium

Chlorosulphonyl isocyanate (226 ml) was added to a solution of triethylamine (10 ml) in methyl acetate (3.8 l). The resulting clear solution was cooled to −15° and a suspension of (6R,7R)-3-hydroxymethyl-7-[(Z)-2-(fur-2-yl)-2-methoxyiminoacetamido]ceph-3-em-4-carboxylic acid (763 g) in methyl acetate (2.3 l), pre-cooled to −15°, was added over 10 minutes. The residual solid was rinsed in with methyl acetate (700 ml). The mixture was stirred at −5° for 30 minutes, a clear solution being obtained after 10 minutes. Water (1.2 l) at 18° was added rapidly to the reaction mixture, the temperature rising quickly to 10° and then slowly to 17°. The mixture was stirred for 60 minutes at 15° to give a thick, white suspension. Methyl acetate (3.6 l) was added followed by a steady addition of a solution of sodium hydroxide (288 g) in water (5.2 l). This gave a clear two-phase mixture at 26° with a pH of 2.35. The layers were separated and the upper, organic layer was washed with a solution of sodium chloride (600 g) in water (2 l). The two aqueous layers were washed sequentially with methyl acetate (2 l). The organic layers were bulked, stirred with Norit SX Plus charcoal (76 g) for 30 minutes and filtered

through a bed of Hyflo Supercel, the bed being washed with methyl acetate (1.5 l). The filtrate and wash were combined and stirred at 20° whilst a solution of sodium 2-ethylhexanoate (338 g) in a mixture of methyl acetate (2 l) and water (40 ml) was added over 20 minutes to give a white suspension with a pH of 5.5. The suspension was stirred for 10 minutes and filtered, and the cake was washed with methyl acetate (5×1 l), sucked dry, and dried at 30° in vacuo for 24 hours to give cefuroxime sodium (851.9 g); $[\alpha]_D^{20}$ +60°, (c0.5; 0.1M pH 4.5 buffer); λmax (H_2O) 273 nm ($E_{1\ cm}^{1}$% 387); impurities by HPLC 2.0%.

PREPARATION 2

Crystalline Cefuroxime Axetil

(RS)-1-Acetoxyethylbromide (12.5 g) was added to a stirred mixture of sodium cefuroxime (20 g) in dimethyl acetamide (110 ml) at 0° C. The mixture was stirred at +1° for 90 minutes and potassium carbonate (0.5 g) was added. Stirring was continued for a further 2 hours at 1°-3° when the reaction mixture was added to a rapidly stirred mixture of ethyl acetate (200 ml) and aqueous 3% sodium bicarbonate (200 ml) to destroy any excess 1-acetoxyethylbromide. After 1 hour the organic layer (1.5% Δ^2 isomer by HPLC) was separated, washed with N hydrochloric acid (100 ml) and aqueous 20% sodium chloride containing 2% sodium bicarbonate (30 ml). All three aqueous phases were sequentially washed with ethyl acetate (100 ml). The combined organic extracts were stirred for 30 minutes with charcoal (NOrit SX Plus; 2 g), filtered through a kieselguhr bed which was washed with ethyl acetate (2×25 ml). The combined filtrate and washes were evaporated in vacuo to 150 g and stirred at ambient temperature for 1 hour until the crystallisation was well established. Di-isopropyl ether (250 ml) was added over 45 minutes to complete the crystallisation and stirring was continued for an additional 1 hour. The product was collected by filtration, washed with 2:1 diisopropyl ether/ethyl acetate (150 ml) and dried for a weekend in vacuo at 50° to give crystalline cefuroxime axetil (19.3 g).

Solvent content (GLC) 0.2% m/m. Impurities by HPLC 1.8% Isomer ratio (HPLC) 1.0:1. $[\alpha]_D$ (1% in dioxan)+37°; $E_{1\ cm}^{1}$% (278 mm, MeOH) 389.

The individual R and S isomers of cefuroxime 1-acetoxyethyl ester are denoted for convenience by the letters A and B, these letters being used to denote the respective isomers as in British Patent No. 1571683. The identities of isomers A and B have not been assigned. The isomer ratios given in the following Examples are expressed as A:B. Temperatures are given in °C. The values given for $E_{1\ cm}^{1}$% and $[\alpha]_D$ are not corrected for solvent content.

EXAMPLE 1

A 10% m/v acetone solution of a mixture of R and S isomers of cefuroxime axetil was put through a Niro Mobile Minor Spray Drier, supplied by Niro Copenhagen, Denmark, using air as the drying gas and a rotary atomizer running at about 35,000 rpm. The gas inlet and outlet temperatures were 124° and 70° respectively. A recovery of 75% m/m of spray dried product was obtained. The microscopic appearance was typical for a spray dried product (hollow spheres). Assay by HPLC was 97% m/m and impurities by HPLC 2.0% m/m, both calculated to dry from a measured solvent content of 0.15% m/m (GLC), and a water content of 0.8% m/m (Karl Fischer). The isomer ratio was 1.04:1 (HPLC). Infrared spectrum (Nujol), ν_{max} 3480-3210 (NH,NH_2 complex), 1782 (β-lactam), 1760 (acetate), 1720 (4-ester group), 1720 and 1594 (carbamate), and 1676 and 1534 cm^{-1} (7-amido); $[\alpha]_D$ (dioxan)+38°; $E_{1\ cm}^{1}$% (MeOH) 398. X-ray powder analysis in a 0.3 mm diameter capillary by the Debye Scherrer method in a 114.6 mm diameter camera by exposure for 3 hrs. to CuK_α radiation gave a plain halo (absence of crystals, confirming the amorphous nature of the product).

EXAMPLE 2

A mixture of R and S isomers of cefuroxime axetil (20.25 g) was dissolved in acetone (200 ml) at ambient temperature. The solution was clarified through sintered glass and pumped through a two fluid atomizer jet, using nitrogen under 1 kg/cm² as the atomising fluid, into the glass drying chamber of a Mini Spray HO spray drying apparatus using an approximately 50:50 mixture of air and nitrogen as the drying gas. The gas inlet and outlet temperatures were 75° and 55° respectively. The recovery was 14.1 g (70.5%) of amorphous material containing 1.1% m/m acetone (GLC). Impurities (by HPLC) 1.7% m/m including 0.2% m/m ceph-2-em compound. Isomer ratio 1.03:1. ν_{max} (Nujol) similar to that shown in FIG. 1. $[\alpha]_D$ (dioxan)+35°; $E_{1\ cm}^{1}$% (MeOH) 386.

EXAMPLE 3

A 15% acetone solution of cefuroxime axetil (ca 1:1 mixture of R and S isomers) was put through a closed cycle spray dryer using nitrogen as the recycling gas and a rotating wheel atomiser running at 24,000 rpm. The gas inlet and outlet temperatures were 105° and 70° respectively. The recycling gas was cooled to remove most of the evaporated acetone. Recovery of amorphous product was 90% with an acetone content of 1.0% m/m (GLC), water 0.7% m/m (Karl Fischer), HPLC impurity level 1.3% m/m. Infrared (Nujol) (KBr plates) and nmr spectra (DMSO-d_6) are shown in FIGS. 1 and 2 respectively. $[\alpha]_D$ (dioxan)+38°; $E_{1\ cm}^{1}$% (MeOH) 398.

Further Examples 4 to 17 illustrating the preparation of amorphous cefuroxime axetil are given in the following Table. The process of these examples was similar to that of Example 2. The Nujol infrared spectrum of each of the products was similar to that shown in FIG. 1.

Ex No.	Solvent	Inlet Temp °C.	Outlet Temp °C.
4.	Acetone/water	62	55
5.	Industrial methylated spirit	80	70
6.	Acetonitrile	72	63
7.	Tetrahydrofuran	75	65
8.	Methylacetate	63	55
9.	Chloroform (water sat)	64	58
10.	Acetone/water	70	50
11.	Ethylacetate/water	72	64
12.	Methylacetate/water	64	57
13.	Methanol/water	67-70	55-59
14	Methanol/acetone	63	54
15.	Ethanol/acetone	83	65
16.	Acetone/methylacetate	63	54
17	Acetone	85-90	75

Ex No.	Product Isomer Ratio	Impurities (% m/m)	$[\alpha]_D$ (dioxan)	$E^{1\%}_{1cm}$ (MeOH)
4.	1.05:1	1.8	+35°	390
5.	1.05:1	1.9	+36°	386
6.	1.00:1	1.6	+35°	389
7.	1.04:1	2.0	+34°	384
8.	0.94:1	1.3	+35°	387
9.	1.02:1	1.5		
10.	1.05:1	1.2		
11.	1.02:1	1.4		
12.	0.98:1	1.2		
13.	1.04:1	1.9		
14.	1.03:1	1.4		
15.	1.02:1	1.6		
16.	1.02:1	1.6		
17.	pure B	0.9	+9°	387

EXAMPLE 18

A solution of purified crystalline cefuroxime 1-acetoxyethyl ester (isomer A) (77 g) in acetone (1.8 liters) at 45° was spray dried as in Example 2 through a two fluid atomizer nozzle with a nitrogen atomizing pressure of 0.5 kg/cm². The gas inlet temperature was 85°-90° and the outlet temperature ca 75°. The product (39 g) had an acetone content of 0.15% m/m and impurities by HPLC of 2.8% m/m. The infrared spectrum (Nujol) confirmed the amorphous nature of the product. X-ray powder analysis showed a few faint lines which may suggest the presence of a few crystals. $[\alpha]_D$ (dioxan) +64° $E_{1cm}{}^{1\%}$ (MeOH) 386.

EXAMPLE 19

A mixture of the R and S isomers of cefuroxime axetil (10 g) was dissolved in hot acetone (70 ml) and evaporated in vacuo to a froth. This was broken up and dried overnight in vacuo at 40° to give 9.8 g of cefuroxime axetil which was shown by IR (Nujol) (which was similar to that in FIG. 1) and microscopic examination to be amorphous. The acetone content (GLC) was 2.9%. Impurities by HPLC were 3.4% m/m and the isomer ratio was 1.14:1.

Following the above procedure, pure amorphous cefuroxime axetil was also obtained using IMS, methanol and ethyl acetate as solvents.

EXAMPLE 20

A ca 1:1 mixture of the R and S isomers of cefuroxime axetil (5 g) was dissolved in boiling ethylacetate (200 ml) and concentrated at atmospheric pressure to 70 ml. The solution was kept hot and added dropwise over 27 minutes to rapidly stirred petroleum ether (bp. 60°-80°; 560 ml) maintained below 3°. After the addition the suspension was stirred for a further 10 minutes, filtered, displacement washed with petroleum ether (bp 60°-80°) and dried overnight in vacuo at 50° to give 4.5 g of amorphous cefuroxime axetil. Solvent content (GLC) 0.25% m/m; $[\alpha]_D$ (1% in dioxan) +39°; $E_{1cm}{}^{1\%}$ (MeOH) 388. Microscopic examination confirmed the amorphous nature of the product.

EXAMPLE 21

A ca 1:1 mixture of the R and S isomers of Cefuroxime axetil (6 g) was dissolved in boiling dichloromethane (240 ml), allowed to cool and filtered. The filtrate was distilled to a volume of 55 ml at atmospheric pressure and added dropwise, over 42 minutes, to rapidly stirred di-isopropyl ether (195 ml cooled below 3° C. After the addition the suspension was stirred for a further 15 minutes, filtered, washed with di-isopropyl ether (100 ml) and dried overnight in vacuo at 50° to give 5.5 g of amorphous cefuroxime axetil. Microscopic examination suggested <1% crystalline material. $[\alpha]_D$ (1% dioxan) +36°, $E_{1cm}{}^{1\%}$ 387 (MeOH). Solvent content (GLC), 1%.

EXAMPLE 22

Cold water was fed at a rate of 750 ml min^{-1} into a 5 l plastic beaker fitted with a horizontal aperture just below its top edge. The water was additionally agitated by means of a paddle stirrer (600 r.p.m.) while a stream of nitrogen was bubbled in at 12 l min^{-1}. A solution of a mixture of the R and S isomers of cefuroxime axetil (200 g) dissolved in a warm (45°) mixture of acetone (600 ml) and water (66 ml) was then added with the aid of a peristaltic pump at a constant rate over 13 minutes into the vortex of the water. The precipitated amorphous cefuroxime axetil was carried through the horizontal aperture as a froth and collected. The amorphous cefuroxime axetil product was harvested immediately and dried to constant weight in vacuo at 55° to yield 170 g. Solvent content (GLC) <0.01 m/m. Impurities by HPLC were 1.8%. The isomer ratio was 1.14:1. $[\alpha]_D$ (1% dioxan) +40°; $E_{1cm}{}^{1\%}$ (MeOH) 395. X-ray crystallography revealed the product was substantially amorphous with a small content of crystalline material.

EXAMPLE 23

A ca 1:1 mixture of the R and S isomers of cefuroxime axetil (100 g) was dissolved by stirring in acetone (1 l) and warming to 40°. The rollers of a drier were heated to 75°, steam (two bar pressure) was put on the jacket and 737 mm vacuum applied to the apparatus. Using a roller speed of 1.75 rpm the prepared solution of cefuroxime axetil was sucked in at a rate of ca 200 ml/min. The product was knifed from the rollers and collected in 94% m/m recovery. Impurities by HPLC were 1.1% m/m. Solvent (GLC) content was 1.6% m/m. X-ray crystallography and infra-red (Nujol) indicated that the material was amorphous. The Nujol infra-red spectrum was similar to that shown in FIG. 1.

EXAMPLE 24

A solution of a ca 1:1 mixture of the R and S isomers of cefuroxime axetil (10 g) in dioxan (100 ml) was freeze dried to give the product (10.7 g) which contained dioxan 5.5% m/m after being 40 mesh sieved and oven dried in vacuo at 50° for 20 hours. The infra-red (Nujol) spectrum was similar to that shown in FIG. 1. The infra-red (Nujol) spectrum and microscopic examination confirmed the amorphous nature of the product. $[\alpha]_D$ (1% in dioxan) +37°; $E_{1cm}{}^{1\%}$ (MeOH) 388.

EXAMPLE 25

A slurry of sodium cefuroxime (20 g) in dimethylacetamide (100 ml) was cooled to 14° and (RS) 1-acetoxyethyl bromide (10 ml) was added. The mixture was stirred at 14° for 45 minutes before anhydrous potassium carbonate (0.5 g) was added. After stirring for a further 45 minutes ethyl acetate (200 ml) and 3% sodium bicarbonate solution (200 ml) were added. The mixture was stirred at ambient temperature for 1 hour and the two phases were allowed to separate. The aqueous layer was washed with ethyl acetate (100 ml) and the two organic layers were then washed sequentially with M hydro-

chloric acid (100 ml) and 20% sodium chloride solution (30 ml). The combined organic layers were stirred with charcoal (2 g) for 30 minutes before filtration. The filtrate was concentrated in vacuo to 176 ml. Water (1.9 ml) was added to the concentrate which was run into stirred 60°-80° petrol (1.76 l) over 15 minutes. The precipitated product was filtered off and washed with a mixture of petrol (105 ml) and ethyl acetate (12 ml) followed by petrol (118 ml). Drying at 40° in vacuo gave cefuroxime axetil 17.9 g: Solvents (GLC), ethylacetate 1.6%, petrol 1.5%; impurities by HPLC 4.1% m/m, isomer ratio 1.06:1; $E_{1\ cm}^{1\%}$ (MeOH) 364. The infra-red spectrum in Nujol was typical of the amorphous material.

EXAMPLE 26

Acetone (2000 ml), water (324 ml) and IMS (36 ml) were added to a stirred flask followed by a ca 1:1 mixture of the R and S isomers of cefuroxime axetil (600 g). The contents of the flask were heated to 42° and stirred until the solid dissolved. Immediately prior to use the solution was cooled to 20°.

Water (2000 ml) was added to the precipitation vessel and stirred at 800 rpm. Nitrogen was fed into the solution at the centre of the vortex caused by the impeller at 10 l min^{-1}.

Water (850 ml/min) and the cefuroxime axetil solution (115 ml/min) was added simultaneously into the turbulent zone in the precipitator. The overflow from the precipitator was directed onto a 125 micron mesh screen where the precipitated product, in the form of an aerated slurry, was retained and the clear liquors passed through, to be discarded.

The precipitated product collected on the screen was transferred to a filter fitted with a filter paper for further dewatering. The dewatered product was dried in vacuo at 45° until the moisture content was reduced to less than 1% to yield 410 g of cefuroxime axetil.

The infra-red (Nujol) spectrum confirmed the substantially amorphous nature of the product.

Pharmacy Examples

1. Tablet

Composition	mg/tablet
Cefuroxime axetil according to the invention	300.00 (equivalent to 250 mg cefuroxime)
Starch 1500 (Colorcon, Inc) (Pregelatinised starch)	161.5
Sodium Starch Glycolate	20.0
Sodium Lauryl Sulphate	10.0
Polyethylene glycol 6000 (micronized)	7.5
Silicon Dioxide	1.0
Total weight	500.0

Method of Preparation

The polyethylene glycol, sodium lauryl sulphate, sodium starch glycolate and silicon dioxide were passed through a 60 mesh screen and blended with a small quantity of the active ingredient. This was then blended with the starch and the rest of the ingredients and tablet slugs prepared by direct compression. The slugs were broken down through a 20 mesh sieve and the resulting granules compressed using normal concave punches to a tablet weight of 500 mg.

The tablet may then be film coated with cellulose derivatives with plasticisers, colouring agents and preservatives if necessary, using aqueous or organic solvent methods.

As an alternative to the preliminary slugging stage, the blend may be densified by roller compaction or the blend may be compressed directly into tablets.

2. Capsule

Composition	mg/capsule
Cefuroxime axetil according to the invention	300.00 (equivalent to 250 mg cefuroxime)
Microcrystalline cellulose	24.75
Hydrogenated Vegetable Oil	4.0
Sodium Lauryl Sulphate	9.0
Silicon Dioxide	1.25

Method of Preparation

The active ingredient was densified by roller compaction then consecutively passed through a 20 mesh, 30 mesh and 60 mesh screen. The remaining ingredients were passed through a 60 mesh screen together with a small quantity of the active ingredient and then blended with the rest of the active ingredient.

The blend was then filled into size 0 hard gelatin capsules to a target fill weight of 339 mg.

3. Powder for oral suspension (in sachet)

Composition (per sachet)	
Cefuroxime axetil according to the invention	300 mg
Sodium lauryl sulphate	25 mg
Hydroxypropyl-methyl-cellulose	90 mg
Spray dried orange flavour	150 mg
Castor sugar to	2220 mg

Method of Preparation

The sodium lauryl sulphate, hydroxypropylmethylcellulose and flavour were triturated with the active ingredient. This blend was then further blended with castor sugar, adding the latter in two stages. The correct weight can then be filled into a suitable container e.g. sachet of suitable laminated foil and sealed by heat. Before use the powder is constituted by adding about 15 ml water shortly before administration.

4. Oily Suspension

Composition (per 5 ml dose)	
Cefuroxime axetil according to the invention	300 mg
Lecithin	35 mg
Butylhydroxybenzoate	2 mg
Aluminium monostearate	25 mg
Aluminium distearate	25 mg
Hydrogenated castor oil	17.5 mg
Liquid flavour	25 mg
Icing Sugar	1,500 mg
Sodium chloride	2.5 mg
Fractionated coconut oil to	5 ml

Method of Preparation

Some of the coconut oil was heated, then the lecithin, butylhydroxybenzoate aluminium stearates, hydrogenated castor oil, icing sugar and sodium chloride were added to the oil with mixing.

The mixture was cooled and the cefuroxime axetil and flavour added. The remainder of the required coco-

nut oil was then added and the preparation was mixed and refined.

We claim:

1. Cefuroxime axetil in amorphous form essentially free from crystalline material, and having a purity of at least 95% aside from residual solvents.

2. The product of claim 1 which contains less than 3% m/m of impurities.

3. The product of claim 1 in the form of a mixture of R and S isomers.

4. The product of claim 3 wherein the mole ratio of R to S isomers is from 3:2 to 2:3.

5. The product of claim 3 wherein the mole ratio of R to S isomers is from 0.9:1 to 1.1:1.

6. The product of claim 1 in the form of hollow microspheres.

7. A method of combatting bacterial infections of the human or animal body which comprises administering to the said body orally or rectally an effective amount of a highly pure substantially amorphous form of cefuroxime axetil as claimed in claim 1.

8. An antibacterial pharmaceutical composition containing an antibacterially effective amount of cefuroxime axetil according to claim 1 in admixture with one or more pharmaceutical carriers or excipients.

9. The antibacterial pharmaceutical composition of claim 8 wherein the cefuroxime axetil is present in the form of a mixture of R and S isomers.

10. Th antibacterial pharmaceutical composition of claim 8 wherein the mole ratio of R to S isomers is from 3:2 to 2:3.

11. The antibacterial pharmaceutical composition of claim 8 wherein the mole ratio of R to S isomers is from 0.9:1 to 1.1:1.

12. The antibacterial pharmaceutical composition of claim 8 wherein the cefuroxime axetil is in the form of hollow microspheres.

13. The antibacterial pharmaceutical composition of claim 8 adapted for oral administration.

14. The antibacterial pharmaceutical composition of claim 13 in dosage unit form containing from 50 to 500 mg of cefuroxime axetil.

* * * * *

PROOF OF SERVICE BY OVERNIGHT COURIER

In Re: NONCONFIDENTIAL BRIEF OF DEFENDANT-APPELLANT RANBAXY PHARMACEUTICALS INC.; No. 01-1151
Caption: Ranbaxy Pharmaceuticals Inc. vs. Glaxo Group Limited, et al.
Filed: IN THE FEDERAL CIRCUIT COURT OF APPEALS **(via Federal Express)**

STATE OF CALIFORNIA)
) ss:
COUNTY OF LOS ANGELES)

I am a citizen of the United States and a resident of or employed in the City and County of Los Angeles; I am over the age of eighteen years and not a party to the within action; my business address is: 350 South Figueroa Street, Suite 400, Los Angeles, California 90071. On this date, I served two copies of the above-entitled document on the persons interested in said action by placing sealed envelopes in the service of an overnight courier for next business day delivery, addressed as follows:

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NOTE: Defendant-Appellant files this brief pursuant to FRAP 25(a)(2)(B)(ii): "A brief or appendix is timely filed . . . if on or before the last day for filing, it is dispatched to a third-party commercial carrier for delivery to the clerk within 3 calendar days."

I certify (or declare) under penalty of perjury that the foregoing is true and correct. Service and court filing executed on January 9, 2001, at Los Angeles, California.

E. Gonzales